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ARTERIOVENOUS ANEURYSM OF MID-BRAIN AND RETINA, FACIAL NÆVI AND MENTAL CHANGES.

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THIS paper is a description of a curious association of lesions, consisting of arteriovenous aneurysm of one or both sides of the mid-brain, arteriovenous aneurysm or some similar congenital vascular abnormality of the retina on the corresponding side and cutaneous nævi with psychical changes. Sometimes the mid-brain or retinal lesion occurs alone, so that examples of arteriovenous aneurysms of the retina have been recorded without other abnormalities, but none of these cases have been followed for any length of time.

Very few cases of arteriovenous aneurysms of the mid-brain have been recorded. V. Lehoczky (1924) described, as a cerebellar arteriovenous aneurysm, a case (case 1) in which such a lesion occurred in the dorsum of the mid-brain and was continued into the anterior part of the vermis. Brock and Dyke (1932) described two cases (cases 3 and 8). Yates and Paine (1930) described an arteriovenous aneurysm involving the occipital lobe, the mid-brain, choroid plexus and the Sylvian veins on one side. In addition several other cases have been reported in which it is probable that the mid-brain was the seat of an arteriovenous aneurysm, though not so recognized by the authors. These are the cases of Heitmüller (1904), Northfield (1940-41), Bergstrand, Olivecrona and Tönnis (1936) (cases 13 and 22), Nicolato (1933), Bonnet, Dechaume and Blanc (1937) (case 1), and Ehlers (1925). A brief résumé of these cases now follows.

V. Lehoczky. Male, aged 34. For ten years had attacks of headache, sickness and bradycardia, at first relieved by lumbar puncture but later this lost its effect. Death with symptoms of raised intracranial pressure. Autopsy disclosed an arteriovenous aneurysm of the quadrigeminal plates extending into the anterior part of the vermis. Death due to subarachnoid hæmorrhage. No report on fundal appearances.

Brock and Dyke. Case 3.—Male, aged 21. Mottling of the skin of the right side of the face since birth. Profuse bleeding after dental treatment and tonsillectomy. Since 14 years of age right-sided tinnitus. At 15 years an attack called "acute epidemic encephalitis" in which he slept and was delirious for one month. The right arm and leg were weak and speech impaired, the last-named remaining. On admission ataxia, marked restlessness, fatiguability, depression, mental deterioration, and suicidal trends. *Examination*: "angioma" of the right face; right ear pulsated; murmur over right temporal region, disappearing with compression of the carotid artery; bilateral exophthalmos, more so on the right; engorged vessels in the eyelids with bilateral internal rectus weakness; right eye blind, in the fundus (fig. 8) an "angiomatous" formation with varicosity of the central veins; right external strabismus; speech slow and scanning; left facial weakness on mimetic movement; blood-pressure 110/80. Committed suicide seven months later. Autopsy showed an "angiomatous" mass covering the right part of the optic chiasma, right optic nerve and fundus, mid-brain and right side of cerebellum. The pathological details will be considered later.

Case 8.—Male, aged 34. At 24 years an illness characterized by headache, dizziness and vomiting. In bed three to four months. Diagnosed as "acute epidemic encephalitis." Examination then showed sluggish pupils, weak left internal rectus, nystagmus, bilateral ptosis, paresis of right side of face, diminution of tendon reflexes in upper limbs and absence in lower limbs and urinary retention. Eight months before admission he began to have attacks of loss of consciousness in which the head was drawn backwards, left arm went into clonic spasm and back became rigid and extended. Left arm then went rigid, clonic twitching of the left side of the face occurred and the eyes turned to the left, right arm and legs were also rigid. Unconscious for twenty minutes. Attacks had recently been followed by prolonged confusion. *Examination:* suspicious, euphoric; bilateral papillœdema, with optic atrophy; pupils sluggish to light; power of convergence of eyes lost; left internal rectus palsy; external strabismus; nystagmus on upward and lateral deviation; left homonymous hemianopia; right facial weakness; drawling speech; Romberg's sign positive; slight dysdiadochokinesis on right; deep reflexes diminished; no Babinski response; abdominal reflexes absent; temperature sensation lost on right side as far down as umbilicus and diminished below this on left; C.S.F. normal. Radiography showed slight atrophy of the posterior clinoid processes. Ventriculography showed bilateral hydrocephalus due to obstruction of the aqueduct. Died post-operatively from hæmorrhage. Autopsy showed an arteriovenous "angioma" filling the upper one-third to one-quarter of the mid-brain in the region of the quadrigeminal plate, and extending entirely across this part of the brain stem.

Yates and Paine.—Male, aged 32. Eleven years before he began to experience weakness of right arm and leg. Intermittent severe headache associated with difficulty in speech. Memory poor. At times quarrelsome and violent. Pains localized above the left eye. Vision began to fail. Gait became hemiplegic and tended to fall to left. Attacks of giddiness. *Examination:* dull mentally; slight aphasia; slight left proptosis; right pupil wider than left; right homonymous hemianopia; veins of the left fundus (fig. 7) enormously distended and at the periphery of the upper nasal quadrant was a small aneurysmal dilatation while on one artery near this were three tiny seed-like dilations separated by constrictions; pain was in the first and second divisions of the left trigeminal territory; slight left lower facial weakness; right arm and leg weak and spastic; right plantar reflex extensor; systolic murmur over head; blood-pressure 110/85; no cardiac hypertrophy.

Autopsy disclosed numerous abnormal vessels in left cerebral hemisphere, mid-brain and above left cavernous sinus. Further details will be described later.

Heitmüller.—Female, aged 13. Since birth "tumour" of right orbit, the size of a hazel nut and consisting of dilated branches of ophthalmic artery. Dilatation now extended to occipital region. Hair not grown over affected area. In last six years gradual appearance of left hemiplegia. *Examination:* proptosis of right eye, which looked downwards and outwards; conjunctiva thickened with dilated capillaries; cheeks showed dilated capillaries; right-sided anosmia (presumably due to nasal hyperæmia); right eye blind; right pupil smaller than left, but reacted consensually; left pupil not reacting consensually; right ptosis; right third nerve palsy; right fundus showed closely packed vessels, and arteries indistinguishable from veins; complete left hemianopia, and on right to within 15 degrees of fixation point; right sided deafness; taste not appreciated in right half of tongue; tremor of left hand on movement; left hemiplegia.

Nicolato.—Male, aged 25. Seven months before admission he suffered from "influenza." Two months later sudden onset of weakness of right arm and leg with paræsthesiæ in these limbs associated with vertigo and a sensation of revolving to the right. Fell to ground. No loss of consciousness. Speech disturbance. In next month some return of power in the affected limbs and speech became normal. Three months after, sudden onset of sweating, severe pain in right face, especially mandibular region, with vertigo, but no tendency to fall in any definite direction. Noticed that left eye protruded. Transitory diplopia and rapid onset of blindness in left eye. Dysarthria returned and paresis of the right arm and leg and paræsthesiæ on right side of body increased. Left-handed. *Examination:* mentally retarded; jaw protruded; facial asymmetry; hair sparse on face; blood-pressure 140/80; facial veins engorged on compression of jugular vein, especially those of the temporal fossa which joined the facial vein in a large trunk just behind the outer angle of the orbit; palate deviated to left; right lower facial weakness; right arm and leg smaller than left; right hemiplegia; slight cerebellar signs in left leg; tendon reflexes increased on right; right abdominals diminished; both plantar reflexes extensor; all superficial sensation diminished on right side of the body with some diminution in postural sense on the right side; visual acuity, right 10/10, left finger counting at 50 cm.; left proptosis; left eye deviated outwards; pupils normal; in the left fundus (fig. 9) was an enormous increase in the number and calibre of vessels and issuing from disc was a bundle of vessels; impossible to tell arteries from veins but vessels corresponded roughly to superior and inferior temporal vessels; some vessels left papilla and then looped back to it. In the next two months almost complete disappearance of exophthalmos, but persistence of amblyopia and external deviation of left eye. Hemiplegia and sensory loss remained. C.S.F. pressure and constitution normal. Radiogram of skull showed increased markings. Ventriculo- and arteriogram gave no information.

Northfield.—Male, aged 9. At 10 months noticed that not using right arm and that right leg smaller than left. From age of 3 years head large. At 6 years sudden severe headache and unconsciousness and C.S.F. contained blood under pressure. *Examination at that time:* mental development retarded; dilated veins in both upper eyelids and left cheek; small nævi on back of right leg and above umbilicus; "angiomatous" formation in left retina (fig. 13); visual acuity, right 6/6, left 6/24; non-pulsating proptosis of left eye; slight left ptosis; slight nystagmus; left concomitant divergent strabismus; spastic right hemiplegia with increased tendon-jerks; bilateral extensor plantar responses; right abdominal reflexes diminished; C.S.F. pressure normal, faintly yellow; protein 0·070 grm. per cent.; blood-

pressure 100/70. Radiography showed dilated diplöic vessels in frontal bone. Arteriography showed arteriovenous malformation in territory of left middle cerebral artery. Treated by a course of deep X-ray therapy. One year later symptoms of heart failure appeared with increase in the size and number of veins in the upper eyelids and on the left side of the scalp. Proptosis now pulsating. Bruit heard over the left side of head and neck. Heart enlarged. Blood-pressure 110/70 in right arm. Left common and internal carotid arteries tied with diminution in bruit and size of scalp vessels and lowering of blood-pressure to 92/62. Condition remained improved.

Bergstrand et al. Case 13.—Male, aged 26. Long-continued headache as a child. Fourteen months before admission sudden numb feeling in right arm spreading to leg followed by loss of consciousness for a short time. On admission to hospital could scarcely speak and showed marked paresis of right arm and leg and loss of pain sensation in right half of body. Four days later condition suddenly deteriorated. Temperature rose to 39·2° C. Somnolent. Opisthotonos. Temperature remained raised for a week and, with its fall, psychical manifestations, which had been present, disappeared, but right hemiparesis, hemianæsthesia and hemianopia remained. One year later sudden recurrence of headache and increase in hemiparesis. C.S.F. blood-stained. Two months later examination showed in addition, right facial and palatal weakness. Encephalography revealed dilatation of left lateral ventricle and septum pellucidum slightly displaced to left. Arteriography showed what was thought to be the left choroidal artery considerably enlarged and running backwards into an arterio-venous aneurysm from which a large vein passed into the straight sinus (the radio-gram shows the vascular plexus to lie over the mid-brain). At operation nothing was found at incision into the left temporal lobe and inferior horn and no ab-normality of the choroid plexus could be discovered.

Case 22.—Male, aged 30. Right-side tinnitus for one year. Five months later sudden onset of vomiting, weakness of all limbs and diplopia. *Examination:* bruit over right side of skull; divergent strabismus and ptosis of left eye; bilateral diminu-tion in corneal reflexes; pupils inactive; slight left facial weakness slight bilateral hypotonia in both arms and ataxia of left leg. Arteriography showed the anterior cerebral artery absent and a markedly widened vessel in position of choroidal artery running backwards to be lost in the region of pineal body in a knot of vessels. Internal carotid artery tied, but murmur and tinnitus unchanged and fourteen months later murmur could be heard bilaterally and bilateral optic atrophy preset. with bilateral paralysis of the 3rd and 6th cranial nerves and involvement of the left 5th. Both plantar responses extensor. All deep reflexes very brisk. Sensation normal. Right common carotid artery tied with some improvement in patient's con-dition.

Bonnet. Case 1.—Female, aged 23. Poorly developed mentally. At 7 years left eye found blind. At 12 years sudden onset of right hemiparesis with speech disturbance, following which patient tended to fall to the right and tired easily. Left frontal headache. *Examination:* œdema of upper eyelid; slight left proptosis; dilata-tion of conjunctival vessels; bossing of skull in left parietal region; temporal hemianopia in right eye; slight left divergent strabismus; left pupil paralysed and widely dilated; left fundus showed extraordinary dilatation of retinal vessels, which were very tortuous and papilla very congested without true œdema; visual acuity too low to confirm hemianopia in this eye; C.S.F. pressure 25 (Claude) and contained 0·03 grm. per cent. of protein. Skull radiographs normal. Remained sleepy and mentally retarded but could read and write. Hemiparesis improved but right deep reflexes remained increased and dysdiadochokinesis present in right hand. Exoph-

thalmos and strabismus disappeared and left visual acuity improved to 1/50. Two years later headaches became more severe but was less sleepy. At 25 years examination showed: obese; left eye as before, except now completely blind; papilla less-œdematous, but lost in congested œdema of retina; three pigmented black areas in contact with extremely tortuous vessels (fig. 11); left divergent strabismus; right corneal reflexes diminished; right pupil normal, but left dilated and inactive to light; right hemiparesis and diminution in sense of touch and other superficial sensations on right side; pulsatile subcutaneous "angioma" of left suborbital regions of the face; "angioma" of left upper lip; soft "tumour," probably an enlarged vessel above left eyebrow; several small pigmented nævi on body especially in left axilla. Radiograph showed increased vascular markings of the skull.

Ehlers.—Female, aged 65. Mistiness of vision, flashes of light before the left eye and bilateral ptosis developed in last year. In the left eye was an arteriovenous aneurysm of fundus involving inferior temporal artery and vein. No spontaneous pulsation was seen (fig. 6).

Certain comments are necessary about the cases of Heitmüller, Nicolato, Northfield, Bergstrand, Bonnet and Ehlers. In Heitmüller's and Nicolato's cases the physical signs obviously indicate a mid-brain lesion. The former also postulated a lesion of the anterior cerebral artery to account for the unilateral anosmia. This, however, was probably due to local nasal hyperæmia, resulting from the dilated vessels around the orbit. In Northfield's case the physical signs pointed to a predominantly left-sided mid-brain lesion, but there was a bilateral Babinski response indicating that both sides of the mid-brain were affected. However, he stated that there was an arteriovenous aneurysm in the territory of the middle cerebral artery on one side, which obviously could not explain the physical signs. The chief lesion must have involved the mid-brain and the arteriograms probably demonstrated, either the dilatation of the other cerebral vessels, which often accompany the dilatation of the vessels of the mid-brain, or possibly another arteriovenous aneurysm. In Bergstrand's cases a diagnosis of arteriovenous aneurysm of the choroidal artery was made. According to Moniz (1934) it is not possible to show the choroidal artery by arteriography. The physical signs in the two cases were those of a mid-brain lesion and arteriography showed an arteriovenous aneurysm fed by the posterior cerebral artery. In one case even operation and direct observation revealed no abnormality of the choroid plexus. It seems probable that their diagnoses were incorrect and that the lesions were in fact aneurysms of the dorsum of the mid-brain. In Bonnet's case 1, although no attempt was made to localize the intracranial lesion, the presence of a left external strabismus, diminution of the left corneal reflex, right hemianopia, right hemiplegia and the interference with touch and other superficial sensations on the right side of the body must place the lesion in the mid-brain.

In Ehler's case the onset of bilateral ptosis at the time of the visual failure suggests in the light of what follows, that a lesion of the dorsum of the mid-brain was probably present to account for it. In V. Lehoczky's case no neurological findings or retinal appearances were described.

In contrast to the above are the cases described primarily as retinal vascular abnormalities. Few of these have been reported, but in those of Gunn (1884), Kreutz (1903), Bonnet *et al.* (1937) (Case 2; same case as reported by Bethoux, Isnel and Marcoulides, 1936), Schleich (1885), and possibly in the two cases of Gertz (1915-16), there has been evidence of the presence of an intracranial arteriovenous aneurysm, but the authors made no attempt to localize it. A brief account of these cases now follows:

Gunn.—Female, aged 11. Convulsions at the age of one month. At 4 years an illness in which head drawn backwards, became unconscious, and ill for six weeks, towards the end of which time an eruption of small bullæ appeared over left cheek, arm and leg. At 6 years again mentally deranged for two to three days at time of dental abscess. Always very excitable. For the last four years subject to severe headache coming on two or three times daily, lasting a quarter to two hours and associated with nausea and vomiting. Pain chiefly vertical and occipital. During attack the face became grey and pinched. Headaches brought on by excitement. *Examination:* intelligent nervous child with wide active pupils; in the right eye were two cilio-retinal arteries at outer side of disc; in left fundus (fig. 2) was a large vessel running vertically immediately to inner side of macula, and on tracing downwards it was found to be a branch of the inferior temporal vein, while on passing upwards it bifurcated and one branch continued upwards in the line of the vessel, the other passing upwards and inwards to open directly into the superior temporal artery; several of the retinal veins appeared to commence abruptly, doubtless having their origin in the choroid. In one case a vein began thus, soon attaining a large size and dark colour while further on it became much smaller again before entering inferior nasal vein. Visual acuity 20/20 in both eyes. The father and his family were very nervous. One or two of them had peculiar mental symptoms.

Schleich.—Male, aged 8. Two months previously found to be blind in right eye. The superior and inferior temporal vessels of right fundus (fig. 3) were found to form an arteriovenous aneurysm and small aneurysms were found on the vessels. Right pupil larger than left and failed to react to direct light. Murmur present on auscultation over affected eyeball. Left eye normal.

Kreutz.—Female, aged 28. For last three years visual failure of right eye. *Examination:* right-sided pulsating exophthalmos, pulsation also extended to right eyelid and right ear. An arteriovenous aneurysm of head and neck was present in area supplied by both internal and external carotid arteries on right. Right fundus showed greatly elongated tortuous vessels forming a small bundle between macula and disc. It could not be made out whether a direct arteriovenous communication was present. Vision reduced to half normal. Common carotid artery ligatured without effect. No description of the nervous system given.

Bonnet. Case 2.—Female, aged 17. Mother, grandmother and patient had a vascular nævus in right fronto-parietal region. At 10 years sudden illness with meningitic symptoms, left hemiplegia and presence of blood in the C.S.F. From that time vision in the right eye impaired and blindness gradually became complete

although hemiplegia improved. External strabismus of this eye appeared and during this period had attacks of headache, nausea and vomiting relieved by lumbar puncture. At 17 years right eyelid was swollen, and invaded by medium sized dilated tortuous vessels. Murmur heard over right eye. Slight right exophthalmos. Pupils reacted normally. Right fundus (fig. 12) showed a pale disc with very dilated tortuous vessels, a bundle of enormous sinuous vessels emerging from the papilla. Macular region showed a diffuse blackish grey area. Two vascular loops ran round towards it but turned away before reaching it. Direct communication between artery and vein was present. Vision reduced to light perception only. Complete left hemiplegia. C.S.F. pressure 58 (Claude). Protein 0·030 grm per cent. Radiographs showed right ventricle pushed downwards and deformed. X-ray therapy instituted. Later right pupil found large and inactive to light.

Gertz. Case 1.—Female, aged 21. Shortly before, noticed visual failure in left eye. An arteriovenous aneurysm of the inferior temporal vessels was present. She was nervous and excitable.

Case 2.—Female, aged 37. Dimness of vision of the left eye for several months. Visual acuity 5/6. An arteriovenous aneurysm of inferior temporal vessels was present. Nervous and over-anxious.

Comments are also necessary on some of these cases. In Gunn's case it is obvious that the patient had suffered from a subarachnoid hæmorrhage on one occasion, although no clue to its site of origin was given. In Schleich's case the presence of a murmur on auscultation over the affected eye was probably indicative of an intracranial arteriovenous aneurysm. In Kreutz's case no neurological findings were mentioned and, although it was obvious that an intracranial aneurysm was present, no suggestion as to its site was made. In Bonnet's case 2, the presence of an external strabismus of the right eye coupled with a left hemiplegia suggests the lesion was in the mid-brain. In Gertz's two cases, although there was no direct evidence of an intracranial lesion, in the light of the discussion to follow the psychical symptoms were perhaps evidence that such was present.

In addition to those already mentioned, five further examples of retinal arteriovenous aneurysms without other symptoms have been described. These are the cases of Magnus (1874), Seydel (1898), Rentz (1925), Stokes (1934) and Kravitz and Lloyd (1935). (Weve's case (1923) has been mentioned by some authors as an example of this disease, but in his view it was of an entirely different nature and from the description given this would certainly seem to be so. Fuch's case (1882), which was described as a retinal arteriovenous aneurysm is now known to be an example of V. Hippel's disease.) Here follows a short description of these cases.

Magnus.—Male, aged 29. Loss of vision in right eye for two years. Superior temporal and inferior nasal retinal vessels were affected. Some degeneration of

retina in the neighbourhood. A direct arteriovenous communication was present. The pupil failed to react to direct light and the eye was completely blind (fig. 1).

Seydel.—Male, aged 18. Dimness of vision of left eye. Visual acuity 6/9. Superior temporal vessels affected. A direct arteriovenous communication was present (fig. 4).

Rentz.—Male, aged 23. Failure of vision of right eye. Visual acuity 5/35. A mass of vessels were present near the papilla. A direct arteriovenous communication was present (fig. 5).

Stokes.—Female, aged 10. Pupils and sight normal. In left eye was a direct communication between superior temporal artery and inferior temporal vein, the latter being three times the normal size (fig. 10).

Kravitz and Lloyd.—Female, aged 32. In right eye were many abnormal vessels in which it was impossible to tell arteries from veins. The vessels were five times the normal size. An arteriovenous communication was seen in the lower part of the retina.

The subsequent history of none of these five cases was followed and they may have developed neurological symptoms later.

Thus in four or possibly six of the eleven reported cases of retinal arteriovenous aneurysms and associated vascular anomalies there has been evidence of an intracranial aneurysm, but only in that of Bonnet (case 2) have neurological data been given. (The papers of Weskamps and Cotlier (1939, 1940), and Mozzetti (1939) are unfortunately unavailable owing to war conditions, but the former apparently describe a case in which intracranial and retinal arteriovenous aneurysms were associated with a facial nævus, while Mozzetti recorded the association of a retinal arteriovenous aneurysm and a cirsoid aneurysm of the face and neck (presumably due to an intracranial arteriovenous aneurysm).) In all cases with adequate neurological descriptions the cerebral lesions have been in the mid-brain. If Weskamp's and Mozzetti's cases are included, in 15 of the 20 examples of arteriovenous aneurysms of the retina, there has been evidence of an intracranial arteriovenous aneurysm and, conversely, of 11 cases of arteriovenous aneurysm of the mid-brain, 7 have shown retinal vascular anomalies on the corresponding side (in V. Lehoczky's case no reference to the optic fundi was made). Seven examples of this association and two examples of an isolated mid-brain arteriovenous aneurysm are added.

Thus, of the 27 cases of retinal arteriovenous aneurysm or similar anomalies, in 22, i.e. about 81 per cent., there has been evidence of an intracranial arteriovenous aneurysm and in all 14 cases in which adequate neurological examination had been carried out this lesion was probably in the mid-brain. In the 5 cases in which no evidence of an intracranial lesion had been mentioned no subsequent history or neurological data

were given. Of the 20 cases of arteriovenous aneurysm of the mid-brain, in 14 cases, i.e. about 70 per cent., there have been retinal abnormalities. It is thus apparent that the presence of a retinal vascular anomaly is striking evidence for a co-existing arteriovenous aneurysm of the mid-brain, whereas, in about three-quarters of the cases of arteriovenous aneurysm of the mid-brain, a co-existing retinal abnormality has been present.

Pathology.—The pathological descriptions are only available in the cases of Brock and Dyke, V. Lehoczky, Yates and Paine, and in two of my own series (7 and 8). When fully developed, as in Brock's case and Case 7, the abnormal vessels extend as a tract of reddish vascular tissue on *one* side from the retina, covering and permeating the optic nerve, chiasma and optic tract and lying above the cavernous sinus. Posteriorly it reaches the dorsum of the mid-brain chiefly on one side. The quadrigeminal bodies, brachia conjunctiva and red nucleus are permeated. From here the lesion may extend forwards and laterally to involve the pulvinar and posterior hypothalamic region, and backwards in the cerebellar peduncle to involve the anterior part of the vermis, arbor vitæ and dentate nucleus of the cerebellum on the corresponding side. The abnormal vessels may extend laterally from the mid-brain into the choroid plexus as in Yates and Paine's case. The whole of the tract may not be present, but only the posterior portion as in V. Lehoczky's case and in Case 8. In Brock's case 8 only the dorsum of the mid-brain was involved. In Case 8 the dorsal portion of one side of the mid-brain was permeated by vessels of all sizes (figs. 19-21). These extended caudally into the upper part of the pons, and rostrally to the posterior portion of the thalamus and hypothalamus. A large hæmorrhage lay ventral to the aneurysm. In Brock's case 8 the upper third to fourth of both sides of the mid-brain was affected, the lesion extending entirely across the brain stem.

When the abnormal vessels extend forward from the mid-brain, they lie around and within the optic tract on the affected side, and enlarge the corresponding half of the optic chiasma, optic nerve and tract, obscuring the outlines of these structures and tend to produce atrophy and gliosis. This vascular tissue lies above and communicates with the cavernous plexus on that side. In Brock's case 3 and Case 7 the vascular tissue extended in the optic nerve right up to the affected retina. In Yates case, however, the tissue stopped short in the region of the stem of the Sylvian fissure and was joined by a large vein lying in the fissure. The hemianopia, which is often present, may be due to involvement of either the optic tract or the pulvinar, as it was present in Brock's case 8, in which the lesion did not extend into the optic tract.

The afferent vessel to the mid-brain aneurysm in Case 8 was a special branch of the basilar artery and the efferent vessels drained into the straight sinus. In the other autopsy reports no mention is made of this point. In the two cases of Bergstrand *et al.* the afferent vessels apparently arose from the posterior cerebral artery, and, in their case 13, the efferent vessels also drained into the straight sinus, but it is not possible to determine this point in the arteriogram of their other case. The basilar and vertebral arteries were enlarged in Case 8 and the posterior inferior cerebellar artery came off from the lower part of the basilar forming a loop over the anterior border of the cerebellum before winding round to the 4th ventricle region. In the case of Yates *et al.* the basilar artery divided into left and right posterior cerebral arteries, but the former was about three times the size of the latter. The posterior choroidal branches and the calcarine branch of the artery were correspondingly enlarged. A similar relationship was shown by the right and left veins of Galen, and the choroid plexus of the left lateral ventricle was replaced by a twisted worm-like mass of dilated vessels. In Case 8 the jugular bulb on the affected side was particularly large and deeply grooved the petrous bone. In Yates and Paine's case other anomalies were present. "The left side of the brain was smaller than the right. A venous channel passed from the left lateral sinus across the left dural space to reach the left occipital pole, where it ramified over the left occipital lobe, the smaller venous channels occupying the sulci of the cortex in this region, some of the branches entering the substance of the occipital lobe. From the Sylvian fissure ran a large distended blood-vessel corresponding to the superficial Sylvian vein and passed downwards, backwards and inwards to empty into the large venous space immediately above and communicating with the cavernous sinus. A large tortuous venous channel ran from here backwards, close to the surface of the brain and passed lateral to the 5th nerve between its point of emergence from the brain-stem and the Gasserian ganglion. At a point where it crossed superior to the posterior cerebral artery it was joined by another large venous channel, which communicated anteriorly with the superficial Sylvian vein, which passed over the antero-inferior surface of the left temporo-sphenoidal lobe. After receiving this tributary the vessel continued backwards lateral to the general line of emergence of the cranial nerve roots skirting the side of the mid-brain until it reached the region of the posterior portion of the splenium of the corpus callosum. A large communicating vessel branched from it here and ran inwards to join the vein of Galen, which was also greatly enlarged. Subsequently the vessel passed backwards and entered the substance of

the brain through the left calcarine fissure, where it broke up into a number of smaller vessels finally opening into numerous venous spaces within the substance of the occipital lobe."

In Cases 8 and 9, the vessels elsewhere on the surface of the cerebellum and cerebrum and the dural sinuses were distended but not thrombosed, and, in the case of V. Lehoczky, the posterior surface of both halves of the cerebellar hemisphere was covered with markedly widened vessels. This may be the explanation of the radiographic appearances in Northfield's case, where the middle cerebral vessels appeared dilated. It is probable that, as arterialization of the mid-brain lesion progresses, more of the neighbouring blood-vessels become affected and hence, in most cases, this involves the choroid plexus on that side and may lead to over-secretion of C.S.F. and thus contribute to the hydrocephalus, which may be especially marked on the affected side (see later).

Histologically the affected portions of the brain and the optic nerve consist of many tortuous widened blood-vessels, between which lies nervous tissue showing various degrees of gliosis (figs. 22-23). The vessels have for the most part the appearance of arteries, though some look venous, and, in other places, what appear to be dilated capillaries are found. Blood clot may be found in some of the vessels. Most of the vessels are considerably dilated and their walls thinned. There is much branching and intercommunication of vessels. The walls are very uneven in calibre, being on one side thick and showing a well-marked internal elastic membrane, while on the other they may be thin and the membrane absent, thus resembling the structure of veins. The interna in most vessels is composed of a layer of flat cells in a thin layer of delicate connective tissue fibres, and smooth muscle fibres and a well-developed internal elastic membrane may be seen. In many vessels the intima is much thickened, vacuolated, fibrosed and occasionally hyalinized, and in some places a large nodular ingrowth into the lumen of the vessels is present. Where the intima is thickened, the internal elastic membrane may show marked reduplication and fragmentation, but in other areas it is much thinner or absent. The media consists of circularly arranged smooth muscle fibres. It is of varying thickness and may only be distinct in some of the larger vessels. The adventitia varies considerably in thickness. Some of the large vessels are apparently formed as a result of aneurysmal dilatation of smaller ones. The walls are markedly fibrosed, hyalinized and vacuolated so that the layers cannot be distinguished. They may show parietal thrombi and in some cases have evidently ruptured. The variation in appearance of the vessels and the difficulty in distinguishing their arterial

or venous nature is explained by the fact that they develop from the remnants of primitive vascular plexuses, in which neither arteries, veins nor capillaries can be distinguished (see later). As the patient grows older these vessels become arterialized, and sometimes it is only when this occurs that symptoms develop. In some cases rupture of one of the thin-walled blood-vessels has occurred, resulting in a hæmorrhage into the brain tissue and the subarachnoid space, and this may recur on a number of occasions. Blood is then found in the subarachnoid space either at lumbar puncture or autopsy. The abnormal vessels may encroach on the aqueduct causing blockage, and hydrocephalic dilatation of the lateral and 3rd ventricles. For some reason the former are more dilated on the side of the lesion. When symptoms occur early in life there is a resultant considerable enlargement of the skull, e.g. Case 7. Hydrocephalus has been present in all cases reaching autopsy and was shown by encephalography and ventriculography in one of Bergstrand's cases, one of Bonnet's and in Northfield's case. In life it is possible that intermittent blockage occurs by variations in the filling of the abnormal vessels. This accounts for the subsidence of the papillœdema and hydrocephalic symptoms, which may take place, e.g. Case 8.

Besides the changes in the brain the extraordinary increase in the size and number of blood-vessels affects the skull bones. This, of course, is not confined to arteriovenous aneurysms of the mid-brain, but is common to any similar intracranial lesion. The bones are eroded and thinned, in some cases to such an extent that the inner table of bone is completely absorbed, exposing the diplöe. The diplöic vascular channels may be more prominent than usual. The grooves on the bones for the venous sinuses are very much deeper than normal, especially those of the petrosal and lateral sinuses. There is enormous enlargement of the various foramina in the base of the skull, especially the foramina jugulare, ovale and lacerum. The last is usually greatly increased in size and its cartilage absorbed. This erosion may extend to the apex of the petrous bone. The changes may be visible in radiograms of the base of the skull, whereas none are found in the antero-posterior or lateral views.

The eye containing the retinal anomaly is usually proptosed, as in the cases of Kreutz, Bonnet, Yates, Heitmüller, Northfield, Nicolato and in Cases 5, 6 and 9. In later cases the other eye may also be affected, but to a lesser degree, and the affected eye may pulsate as in cases of carotid-cavernous aneurysm. It seems probable that the proptosis is due to the increase in size of the retro-ocular blood vessels in and around the optic nerve, forming part of the tract of "angiomatous" tissue leading

back from the retina to the mid-brain. The proptosis is reducible and may be transient and only occur at the time of a vascular accident such as a thrombosis, as in Nicolato's case. Pulsation occurs when this tract becomes arterialized.

Ophthalmoscopic appearances.—In most cases, in the fundus on the side of the lesion of the mid-brain there is a congenital vascular anomaly. This varies somewhat from case to case. Usually there is a direct arteriovenous communication between an enlarged and tortuous artery and vein. This usually affects the temporal vessels, especially the inferior. Such a communication was described in the cases of Magnus, Schleich, Gunn, Stokes, Kravitz and Lloyd, Kreutz, Rentz, Ehlers, Bonnet (case 2), Nicolato, and in Cases 2, 3 and 6. Often small sac-like or spindle-like dilatations can be found on the affected arteries (Schleich, Seydel, Yates and Paine, and in Cases 2, 3 and 5). Cilio-retinal communications may be found (Cases 5 and 6 and that of Gunn). Occasionally small areas of retinal degeneration and pigmentation are to be found (Magnus, Ehlers, Gunn, Bonnet, and in Case 4). Optic atrophy has not been a feature of any case. No pulsation is visible in the affected vessels. In other cases, instead of, or in addition to, a direct arteriovenous communication there is a very great increase in the number, size and tortuosity of the blood-vessels, such as occurred in the cases of Yates, Bonnet (case 2) and in Case 1. The whole retina seems filled with vessels and it is impossible to distinguish arteries from veins. From the fact that the vessels are the result of maldevelopment of a primitive plexus (see later) it would be expected that their structure would be abnormal. When a vascular retinal anomaly is present the visual acuity varies from nil to normal. In some cases sudden visual failure is the first manifestation of the disease. This is obviously due to a vascular accident, but whether this occurs in the retina or in the abnormal retro-ocular vessels it is not always possible to determine. In some cases, in the absence of retinal anomalies, papillœdema has developed in association with hydrocephalic symptoms.

Histological examination of the retina has been made in only one case (Brock case 3, reported by Krug and Samuels (1932)). The retina showed an unusually well-developed system of blood-vessels just behind the area serrata. The retinal blood-vessels in this region were larger than normal. In the posterior segment the vessels attained so great a size and became so tortuous that they occupied more or less the entire thickness of the retina. They protruded far into the vitreous cavity. Between the walls of the blood-vessels, the attenuated retinal tissue was in a high state of cystic degeneration. At the entrance of the optic nerve many thin-walled

vessels were found distended with blood. Most of them had the structure of veins rather than arteries. The stem of the optic nerve appeared to be converted into a tangle of blood channels lined by endothelial cells and mostly having thin atypical walls similar to cavernous tissue.

Nævi.—Vascular nævi have been described in several cases. They are usually in the trigeminal distribution and always on the side of the affected eye. In Bonnet's first case a pulsating nævus was found below the eye and on the upper lip. A similar nævus was found in the cases of Northfield, Heitmüller and Brock (case 3) and in Case 8, and apparently in the cases of Weskamps *et al.* and Mozzetti. In Bonnet's second case there was a nævus in the fronto-parietal region, and both the mother and grandmother of the patient were similarly affected. In Northfield's case other small vascular nævi were found just above the umbilicus and on the back of the leg. Besides vascular nævi, pigmented nævi may be found at least as commonly. In Bonnet's second case numerous pigmented spots were found in the skin, especially in the axilla. In two cases of my series (4 and 7) similar nævi were found. In one of them (7) a curious diffuse brown pigmentation of the forehead appeared during the illness and remained.

Other congenital anomalies.—In Case 8 the thenar muscles were absent on one side. Skeletal anomalies are also found. In Nicolato's case and in Case 3 there was facial asymmetry. The face looked acromegalic in Case 4. The arm and leg on the opposite side of the lesion were considerably smaller than on the other side in Case 4 and in Northfield's and Nicolato's cases. In Case 7 there was hydrocephalus, a malformation of the distal phalanx of the index finger, spina bifida of D4-6 vertebræ and absence of one kidney. In Case 8 six lumbar vertebræ and a Meckel's diverticulum were present. Case 2 had undescended testes.

Ætiology.—The anomalous vessels are obviously of congenital origin. The presence of congenital defects of bone, muscle, kidney, &c., in some of the cases relates the disease ætiologically to these latter defects. In another paper I hope to show that vascular malformations form part of a large group of related mesodermal and ectodermal defects and may be the only manifestations ("forme fruste") of a gene substitution, which usually results in bone and muscle defects. The condition is dominant and is not sex-linked. Because the disease may manifest itself in a large number of ways it is very unlikely that direct inheritance of an arterio-venous aneurysm of the mid-brain and retina would occur, but, if the related anomalies are sought in members of the patients' families, they can however usually be found.

Embryological considerations.—In order to understand the true nature of the disease described it is necessary to recall the mode of development of the cerebral vessels, for an account of which reference is made to the work of Streeter (1918), whose views are summarized in fig. 24. He points

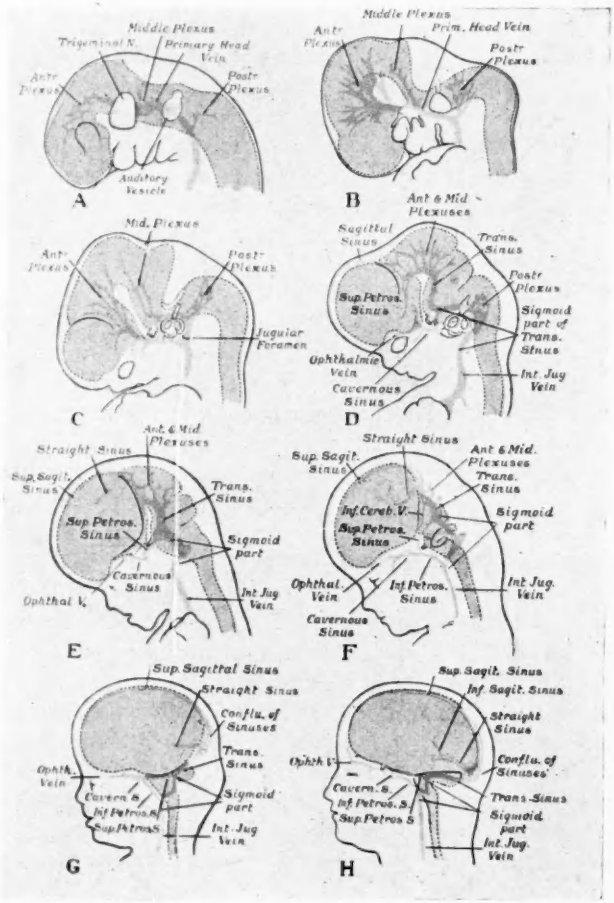

FIG. 24.—Stages in development of cerebral vessels (after Streeter).

A. 4 mm.	B. 14 mm.	C. 18 mm.
D. 21 mm.	E. 35 mm.	F. 50 mm.
G. 80 mm.	H. at birth.	

out that there are five periods in the development of the cerebral blood-vessels in the paraxial mesoderm and these show the special adaptation of the vessels to their changing environmental conditions. In the first period three primordial vascular plexuses are established, the anterior, middle and posterior. In the second period these slowly resolve themselves into arteries, veins and capillaries, recognizable largely by their communications. This period ends at about the 5-7 mm. stage. The third period is characterized by a splitting of the vascular mesoderm into three superimposed layers by the development of the dura mater and cranium, so that superficial, dural and pial circulations result. This stage is present at about 12 mm. The fourth period sees a series of changes in the arrangement of the vascular trunks, and in the fifth period occur the late histological changes, which result in the structure of adult arteries and veins. These stages overlap considerably. It is in the last period that defects occur which later give rise to the common congenital aneurysms on the circle of Willis. At about 2-4 mm. the optic pits form as paired lateral out-pouchings of the anterior end of the primitive neural tube. At this time the anterior end of the neural tube is still open and, when it closes, these evaginations enlarge and, associating themselves with the surface ectoderm, they form two lateral projections on the ventro-lateral aspect of the brain. Surrounding each is the developing paraxial mesoderm covering the anterior part of the primitive neural tube. The development of the mesoderm constricts the connection of the out-pouchings with the neural tube, so that there results a spherical primary optic vesicle connected with the fore-brain by a narrow optic stalk. Meantime, the part of the vesicle in contact with the surface ectoderm invaginates to form a secondary optic vesicle (4-5 mm. stage). The process commences from below and to the outer side by the formation of a groove involving the under side of the optic cup and stalk (the fœtal fissure). At this stage the fissure is filled by vaso-formative mesodermal tissue similar to and continuous with that encircling the eye and anterior end of the neural tube. This ultimately gives rise to the retinal and hyaloid vessels. The fœtal fissure closes by fusion of its walls at the 12-13 mm. stage. From the figure it is obvious that the mesenchyme within the optic cup is derived from the same tissue as forms the primitive anterior vascular plexus and the separation of the two by the closure of the cup at the 12 mm. stage must have occurred before the stage represented by B in the figure, when the three plexuses drain into the primitive head vein. At this stage any inherent defect of the vessels of the mesenchyme in the anterior plexus would be likely to affect

the retina also, and this defect might extend caudally to involve the middle plexus as well. From Streeter's figures it is seen that these two plexuses lie on the primitive mid-brain and upper part of the pons throughout development. Thus might arise a tract of primitive abnormal vascular tissue extending from the retina via the optic stalk (which later becomes the optic nerve and tract) to the mid-brain, and possibly behind this to the region of the upper medulla supplied by the middle plexus. During Streeter's third stage this abnormal vascular mesenchyme becomes split into three layers and hence the most superficial of these layers may also be affected, resulting in a vascular nævus of the skin overlying the anterior part of the brain.

Age and sex.—Assuming that all cases of arteriovenous aneurysm of retina or mid-brain are examples of a single disease, the following is the age distribution at the onset of symptoms.

Ages.	0-10	11-20	21-30	31-40	41-50	51-60	61-70	total
Male	3	6	10	0	0	0	0	19
Female	5	0	3	3	0	0	1	12
								31

It is thus seen that in almost every case symptoms occurred before the age of 30 and the disease is somewhat more common in males.

Symptomatology.—In some cases the retinal anomalies have been discovered in routine examination before symptoms have appeared. Trauma sometimes precipitates symptoms, as in Case 4. The appearance of symptoms depends apparently on thrombosis in, or hæmorrhage from abnormal vessels. According to the site of the vascular changes so either visual or cerebral symptoms may be the first manifestations of the disease. Visual failure may occur suddenly or gradually. In the former case it is usually accompanied by fairly severe headache and perhaps vomiting and sudden proptosis, possibly indicating that the vascular lesion has extended intracranially along the vascular tract described. In other cases visual failure does not occur.

When the mid-brain lesion is the first to produce symptoms the latter vary with the type of vascular accident. If there is a hæmorrhage, blood usually escapes rapidly into the subarachnoid space giving the typical symptoms of a subarachnoid hæmorrhage, namely severe sudden headache, vomiting, neck rigidity and meningitic signs with or without loss of consciousness of varying duration. If the patient recovers the signs of a mid-brain lesion will be found. The hæmorrhage may be recurrent. If the engorgement and dilatation of the vessels of the mid-brain lesion

causes local œdema and obliteration of the aqueduct, the initial symptoms are those of hydrocephalus with headache, usually vertical in position, vomiting and papillœdema. Such occurred in one of Brock's cases and in one of my own series. The striking feature of the hydrocephalic symptoms is that they tend to disappear with rest, possibly owing to the decrease in the filling of the abnormal vessels. The hydrocephalus is thus typically intermittent in type. If the vascular lesion is thrombotic the symptoms often resemble those of "influenza" or encephalitis lethargica. Thus in Nicolato's case and in Case 1, the patient had a sudden onset of headache, pyrexia and general malaise, while in both of Brock's cases the diagnosis of encephalitic lethargica had been made previously.

Whatever the mode of onset, neurological examination shows the signs of the mid-brain lesion. These are inconstant and depend on whether both or only one side of the mid-brain is affected, the position and extent of the abnormal vessels and the nature of the vascular lesion. Typically, however, Weber's syndrome is present, i.e. a unilateral third nerve palsy with contralateral hemiplegia, but both pyramidal tracts may be involved. It may be partial only, and among various manifestations are diplopia, an external strabismus, ptosis, weakness of upward movement and pupillary abnormalities such as eccentricity, irregularity and deficient reaction to light and on convergence. Pupillary abnormalities have been found in nearly every case, even allowing for the effect of the retinal changes on the light reaction. They may be bilateral. In some cases a bilateral ptosis may occur (Ehlers). In about half of the cases nystagmus is present on lateral deviation of the eyes. In one case (7) there was loss of power of voluntary conjugate upward movement of the eyes, but if the eyes were first allowed to fix an object, which was then moved upwards, movement was possible. This was shown by Holmes (1938) to be due to interruption of fibres coming from the frontal lobe in their passage to the mid-brain. In most cases there is a lower facial weakness on the opposite side to the lesion, but occasionally there is an ipsilateral infranuclear facial nerve palsy. In Case 4 taste was lost on the side of the lesion. Sometimes there is evidence of involvement of the sensory path of the 5th nerve on the same side, either as pain or as anæsthesia in the trigeminal distribution, most commonly in the ophthalmic division. Occasionally tinnitus and deafness may occur. In two cases weakness of one side of the palate was found. In most cases of sudden onset there is considerable speech disturbance, varying from complete loss to dysarthria. Usually there is a peculiar slow drawling character to the speech. This may persist permanently. In the majority

of cases cerebellar signs are found on the opposite or on both sides, but usually in the hemiplegic limbs. In addition there may be a disturbance of both superficial and deep sensation on the same side, as in Northfield's and Bergstrand's cases and in Case 8. In some of the cases a hemianopia, which bisects the fixation point, has been found. Its causation has already been discussed. Occasionally attacks resembling epilepsy occur. One of Brock's cases became unconscious, the head being drawn back and the back arched, followed by rigidity and clonic twitching of both sides of the body. Unconsciousness lasted twenty minutes and attacks were followed by prolonged confusion. Case 7 suffered from attacks in which he became semiconscious. The right arm became stiff, the fist clenched and the right arm and leg became numb. The eyes turned to the right and the right side of the face twitched. There was no tongue-biting or incontinence. The patient was able to answer questions, if pressed. This state lasted about a quarter of an hour and was followed by a period of confusion and disorientation. Case 2 was subject to attacks beginning with a hot feeling in the head, noises in the ear and a feeling of giddiness and faintness. Objects became blurred and seemed to move slightly and light seemed red or green. His legs felt weak, his face flushed, his heart beat forcibly, he sweated profusely and was considerably nauseated. The attacks lasted for a few minutes, but the effects for hours. These attacks resemble the "diencephalic fits" described by Penfield (1929). Case 3 was also subject to short periods of unconsciousness preceded by severe headache. In Cases 1 and 4 and in Bonnet's case 1, great increase in weight occurred in the course of the disease. This was presumably due to hypothalamic disturbance. In late cases the general signs of an intracranial arteriovenous aneurysm make their appearance. A systolic murmur synchronous with the heart beat may be audible to the patient and on auscultation. It usually reaches its maximal intensity over the affected eyeball and sometimes may be heard only in this situation. In other cases no murmur is ever heard. Dilatation and increased pulsation and tortuosity of the vessels of the scalp and of the carotid arteries later appear, especially on the side of the lesion. This causes pulsation of the ear. This dilatation especially affects the vessels around and in the orbit causing pulsating exophthalmos and the appearance of soft compressible peri-orbital or temporal swellings or "tumours" as in the cases of Heitmüller, Bonnet *et al.* (case 2) and Kreutz. The capillaries and veins of the eyelids are markedly dilated and engorged. When the vascular engorgement extends inwards from the orbit to the nasal cavity it produces local hyperæmia giving rise to

anosmia. This was probably mistaken by Heitmüller for a lesion of the olfactory lobe. Last of all appear the general effects of an arteriovenous aneurysm on the general circulation. These consist of cardiac hypertrophy, collapsing pulse, low blood-pressure, especially diastolic, polycythæmia and finally signs of heart failure.

Psychosomatic symptoms.—Remarkable features are the intellectual and psychical disturbances, which have been present in almost every case. These may be divided into temporary, occurring at the onset of the vascular accident in the mid-brain and permanent symptoms which remain afterwards. In the former case the symptoms may return with successive vascular accidents. The acute symptoms consist of delirium, disorientation in space and time, hallucinations of vision, a feeling of malaise like influenza, somnolence or sleep inversion and irritability. Thus Brock (case 3) mentions that at the onset of cerebral symptoms there was delirium and somnolence and this coupled with the cerebral signs led to the diagnosis of acute epidemic encephalitis. Bergstrand (Case 3) describes "psychical manifestations and somnolence." In Case 1 there was a feeling of malaise, somnolence, and intense irritability, if disturbed. One patient (case 4) following a fall which dazed him, suddenly began to talk nonsense. "He could say all that he wanted to say, but he spoke about his home, his school, his games and his friends all jumbled up together, meaning nothing." This lasted for about a week and was followed by a period of lassitude and somnolence.

The permanent mental symptoms can be divided into two kinds, those affecting intelligence and memory, and those showing psychical reaction types. The former have been present in nearly every case and are especially marked when the cerebral symptoms make their appearance in early life, and the earlier the symptoms occur the more marked is the disturbance of the intellect. Thus Brock's case 3 was mentally deteriorated. Yates' case had a poor memory. Mental development was retarded in Northfield's and Nicolato's cases and in Bergstrand's case 1. In Case 7 there was considerable mental retardation and a poor memory (hydrocephalus was present however). Case 2 was slow-witted, unable to concentrate and had a poor memory. Case 4 showed marked impairment of memory and intelligence. Case 9 was slow mentally. The reduction in intellectual activity cannot be attributed to the emotional instability because it may occur independently of emotional reaction. The psychotic symptoms are usually those of the affective reaction types but others show paranoid trends, are suspicious, quarrelsome, violent, of uncertain temper, irritable and talkative, while many show symptoms usually associated with the

psychoneuroes. Thus Brock's case 3 was restless, easily fatigued, depressed and committed suicide, and case 8 was suspicious and euphoric. Yates' case had an uncertain temper, was quarrelsome and tended to be violent. Case 1 showed a marked change in his personality from being kind and considerate to his wife, to marked irritability. His habits became slack He omitted to wash and shave and became talkative and willing to discuss any subject at length. Case 7 was asocial and depressed. Case 2 was dull, easily depressed, languid, lacking in mental and physical vigour, polysymptomatic, introspective and irritable. Case 3 was very depressed, felt no good, a trouble to everyone, irritable and very liable to fall into tears. Case 4 was restless and Case 9 was easily depressed, tired and had lost the joy of living. Thus many different types of psychotic and psychoneurotic reactions may occur in association with mid-brain vascular lesions, a fact on which little emphasis has been laid previously. In all of my series and in many of those in the literature however the mental symptoms have been a marked feature of the clinical picture. Their causation will be discussed later.

Cerebrospinal fluid.—Few reports are available. In the cases of Brock (case 8), Bonnet *et al.* (cases 1 and 2) and Nicolato and in most of my own series the fluid was under normal pressure, but in two of my series it was 210 mm. In most of my series and in that of Northfield the protein content was slightly increased up to about 0·080 grm. per cent. and the fluid was sometimes yellow, whereas it was normal in the cases of Brock (case 8), Bonnet *et al.* (cases 1 and 2) and Nicolato. In those cases in which the fluid was removed at the time of a subarachnoid hæmorrhage (e.g. cases 7 and 8) the pressure has been raised considerably, and the fluid contained blood. In Case 1, in which the fluid was removed some time after the hæmorrhage, hæmobilirubin was found in the cerebrospinal fluid.

Radiography.—In six of my series there were no abnormalities in the lateral or antero-posterior skull radiographs. Brock (Case 8) described slight atrophy of the posterior clinoid processes. Northfield found dilated diplöic vessels in the frontal bone, while in both Bonnet's cases and in that of Nicolato there were increased vascular markings. Case 7 showed an enormous hydrocephalic skull. In Case 9 a film of the base of the skull showed (fig. 25) erosion of the apex of the petrous bones. In Case 8 the pineal shadow was displaced to one side.

Encephalography and ventriculography.—This has been carried out in several cases. In that of Nicolato no abnormality was detected. In Brock's case 8 there was bilateral hydrocephalic dilatation of the ventricles due to obstruction of the aqueduct. In Bonnet's second case the

ventricle on the affected side of the brain was pushed downwards and deformed. In Bergstrand's case 13 there was dilatation of the lateral ventricle on the affected side and the septum pellucidum was slightly displaced to that side. In Case 8 there was symmetrical enlargement of both ventricles. In Case 4 a defect was present in the floor of the 3rd ventricle suggesting a 3rd ventricle tumour (fig. 26).

Arteriography has been carried out in four cases. In Nicolato's case no abnormal vessels were demonstrated. Northfield showed an arteriovenous aneurysm in the territory of the left middle cerebral artery. As mentioned before, this was possibly due to additional abnormal vessels, which cannot have been responsible for the symptoms described. In Bergstrand's case 13 the films revealed what was thought to be a considerably enlarged choroidal artery running backwards into an arteriovenous aneurysm from which one large vein passed into the straight sinus and another forward and laterally. The radiograph shows the vascular plexus to lie in the region of the mid-brain. In his case 22, arteriography showed that the anterior cerebral artery was absent and a markedly widened vessel in the position of the choroidal artery ran backwards to become lost in the region of the pineal body in a knot of vessels.

Course.—Only seven cases have died, and, of these, Case 8 survived five years from the onset of symptoms and Case 7 died at the age of 32 with symptoms for fourteen years, while the four others died in from six to 11 years from the onset of symptoms. Of the cases with neurological signs which were alive at the time of the report, the course varied from seven months to sixteen years with an average of five years. The prognosis as far as sight is concerned is always doubtful as some cases develop unilateral blindness early, while others retain almost normal vision for years.

Treatment.—In Cases 2 and 4 deep X-radiation to the brain was used without improvement. In Northfield's case this treatment was also carried out without improvement and a year later the common and internal carotid arteries on the side of the lesion were tied. This latter produced some amelioration in the patient's condition. Kreutz ligatured the common carotid artery without effect. Bergstrand *et al.* in Case 13 explored the lateral ventricle in an attempt to tie the choroidal vessels on the affected side, but no abnormal vessels were found. In their case 22 the internal carotid artery on the affected side was tied without improvement, and later the contralateral common carotid artery was also tied resulting in some improvement. In Case 9 exploratory craniotomy did not alter the patient's condition. For the retinal lesion, in Case 2, radon seeds were sewn on to the sclera over the region of the retinal arteriovenous anastomosis. The vessels shrunk and visual acuity improved from 6/36 to 6/12.

Differential diagnosis, and relationship to other retinal vascular anomalies.—It is important to distinguish the retinal anomalies from those which may resemble them. In the *late stages of any case of intracranial arteriovenous aneurysm*, the anastomosis between the arterial and venous sides of the circulation becomes well-marked and there may then be widening and tortuosity of the retinal veins. They are not, however, increased in number, are found bilaterally, no direct arteriovenous communication is present and the arteries are unaffected. Such changes were described by Cushing and Bailey (1928) (case 11), Wessely (1933), Bergstrand *et al.* (cases 9 and 17) and Eimer and Mehlhose (1927). Fig. 27 is a drawing of the fundus of such a case. Again in *Sturges-Weber's disease* there may be tortuosity and widening of the retinal veins as in the cases of Schirmer (1860), Sturges (1879) and Horrocks (1883) but the chief changes are found in the choroid. Congenital buphthalmos is often present also. The difficulties in diagnosis are further increased when a trigeminal nævus and a contralateral hemiplegia and hemianopia are present. The symptomatology and radiological appearances of Sturges-Weber's disease however are quite distinct. In *Lindau's syndrome*, angiomata of the retina may occur, and they may be associated with similar lesions of the posterior fossa. The retinal appearances may superficially resemble those in the disease under discussion. However a definite tumour is present and local exudates occur in the retina and, although both afferent artery and efferent vein pass to and from the tumour, they do not anastomose directly, but enter its substance. Small aneurysms may also occur on the retinal arteries. The retinal lesions may be bilateral. The neurological signs however are usually those of a cerebellar or 4th ventricle tumour and not those of a mid-brain lesion.

Apart from retinal angiomatosis, *aneurysms of the arteries* may be found unassociated with either a tumour or an arteriovenous communication. Most of these cases are arteriosclerotic in origin and occur in old people. Thus both Litten (1881) and Lionville (1870) described cases in which small arteriosclerotic aneurysms of the retinal arteries were associated with similar lesions of the small perforating arteries of the region of the internal capsule of the brain. *Congenital aneurysms of the retinal arteries* are extremely rare. Pringle (1917) described a number of small aneurysms on the retinal arteries in both eyes of a man of 23 years in whom vision was normal, while Graefe (1808) reported an aneurysm involving the optic nerve and Sous (1865) one at the disc. The relationship of congenital retinal aneurysms to arteriovenous aneurysms is not clear. They are probably more closely related to congenital aneurysms of the circle of Willis.

Retinal macular colobomota may be associated with abnormal vessels and anastomoses between retinal and choroidal circulations. Such cases have been described by Beaumont (1891), Ledekarl (1934) and Mann and Ross (1929). In Gunn's case and Cases 5 and 6 of retinal arteriovenous aneurysm such an abnormal communication was present. The differentiation of the disease, described in this paper, from congenital intracranial aneurysm of the circle of Willis may be extremely difficult especially in the absence of a retinal lesion, as in both cases there may be a subarachnoid hæmorrhage, hemianopia or a third cranial nerve palsy. As far as can be determined retinal vascular anomalies and nævi do not occur in association with congenital intracranial aneurysms.

Ætiology of pyrexial, hypnotic and mental symptoms.—Experimentally, lesions of the posterior nuclei of the hypothalamus and mammillary bodies cause a fall in metabolism, temperature and heart rate, Horner's syndrome with myosis and ptosis, and a general state of lethargy akin to sleep. Cats tend to become cataleptic. Destruction of the tuber region causes hyperglycæmia, severe gastric atonia, disturbance of heat regulation and the adiposo-genital syndrome. Changes in behaviour in animals have frequently been noted. Lesions of the anterior portions of the hypothalamus tend to produce excited states, while posterior lesions are likely to be accompanied by lethargy, indifference, depression and a tendency towards catatonia (Ranson (1937)).

Clinically, pathological disturbances of sleep and temperature regulation occur when the posterior portion of the hypothalamus is affected. Peptic ulcer is often associated with lesions of the hypothalamus. With lesions of the posterior portion of the hypothalamus there are likely to be psychotic and psychoneurotic symptoms, such as changes in the personality varying from simple depression to outspoken manic states, contamination neurosis, &c. (Bailey and Murray (1928), Alpers (1937), &c.). The lesions so far mentioned are of a chronic nature. Evidence that a mid-brain lesion may give rise to acute mental symptoms such as hallucinations has been brought forward by Lhermitte and Levy (1931), Van Bogaert (1927) and Lhermitte (1932). Lhermitte termed the condition "l'hallucinose pédonculaire." He and Levy described a case of a man who developed a bilateral 3rd nerve palsy and Argyll-Robertson pupils. A few days after the regression of these symptoms he developed dysarthria, mental confusion and hallucinations. At the close of the day, he thought that his room was transformed into a railway or subway car. People entered and he talked to them and knew their thoughts. Autopsy revealed little in the mesencephalon or elsewhere. There was pigmentary degeneration of

the reticular grey matter and degeneration in the oculo-motor nuclei, but none was found in the white matter. Other cases of visual hallucination were described in association with barbiturate poisoning and giving rise to symptoms and signs suggesting a mid-brain lesion. Van Bogaert's case suffered from hallucinations of colour and animals, and Weber's syndrome was present. Autopsy revealed softening of the cerebral peduncles, red nuclei and lower half of Forels decussation. In many cases of mid-brain lesions hypersomnia occurs. L'hermitte suggested that the liberation of the psycho-sensorial automatism, where images appear before a consciousness divested of its critical powers, must be considered as a dream process occurring in the waking state. If a peduncular lesion near the oculo-motor nuclei is capable of producing hypersomnia pure and simple, it is equally capable of dissociating the sleep function and liberating its active component, the dream. V. Bogaert considered that the hallucinatory images were due to a weakening of the sense of reality or of attention to life and thus images and pictures take on an abnormal richness or brilliance, far in excess of normal. Mesencephalic hallucinations were explained by disturbance of the affective state of the individual, due directly or indirectly to disturbances of the regions of the brain, where the vegetative centres are situated and whose role in the defence and integrity of the individual become less and less evident. The disinterestedness in the present situation, tendency to confabulation, weakening of the ego with its partial disintegration and the weakening of the sense of reality and of attention to life, are the characters which are found especially in the hypnotic state. It has been said, "dormir c'est se desinteresser," to sleep and dream is to relax attention from reality, to diminish psychical attention and to scatter before a dulled consciousness, images and representations, which form the capricious and incessantly moving texture of a dream. Such acute symptoms as those described by Lhermitte were present in some cases of my series. In view of the fact that acute and more chronic mental symptoms may occur with a lesion of the posterior portion of the hypothalamus, it seems probable that the symptoms in Lhermitte's cases were due likewise to involvement of the same region. In Cases 7 and 8 and also in those of Brock there was involvement of the posterior portion of the hypothalamus by the arteriovenous aneurysm and it is probable that the lesion in this position was responsible for the mental symptoms and also for the influenzal-like attacks with rise in temperature, sleepiness, sleep inversion, &c. Quantitative intellectual reduction is usually associated with lesions of the frontal lobe and corpus callosum. Its presence in these cases is important as are the emotional and personality changes. From

results of studies of decorticated animals it seems that the cortex exerts an inhibitory influence on the lower centres under normal conditions, so that expressions of rage or excitement and even of other more refined reactions in man are held in check. Where these lower centres are situated is not known definitely, but it seems possible that they might be below the upper mid-brain.

Speech disturbances.—Finally a peculiar type of drawling speech was a feature of many of the cases. In this connection it is worth recalling Sherrington's (1900) observations in the monkey. He found that section of the brain between the anterior and posterior corpora quadrigemina abolishes reflex vocalization. Vocalization integrated at this level has a peculiar long drawn-out quality and is often accompanied by slowly executed reflex movements.

Summary

An attempt has been made to define a condition in which an arterio-venous aneurysm of the mid-brain is found in association with congenital anomalies of the retinal vessels on one side. There is often a tract of vascular tissue connecting the two lesions. A vascular nævus may be present in the neighbourhood of the affected eye.

An embryological explanation of the condition is brought forward. The interpretation of the mental symptoms so often present, and the differental diagnosis of the disease are discussed.

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CASE NOTES.

Case 1.—Anomalous vessels in right retina; subarachnoid hæmorrhage; signs of vascular lesion of right mid-brain; mental changes.

Male, aged 25. Admitted to the National Hospital March 18, 1940, under the care of Dr. Carmichael.

Family history.—Nil relevant.

Present illness.—Eighteen months before admission he had an illness in which there was malaise, irritability and somnolence and in which the face was drawn up on the right side. This cleared up in six weeks. About the middle of January, 1940, the patient developed a "cold in the head" with malaise and dry cough which lasted for a week or so, and early in February he developed an illness which was called "influenza", which lasted for three or four days. He was troubled by severe

headache and acute malaise and when he got up and returned to work he noticed that when he smiled or moved his face the right side seemed to move more than the left. He was well otherwise until the beginning of March, when he began to see double, the images being parallel, upright and one above the other; they were unaffected by the direction of the gaze. About the end of the first week in March he gradually noticed that his left hand was weak and he dropped a book he was holding. A few days later he seemed to be unsteady on his feet with a tendency to deviate to the right. All symptoms had progressed. For the last two or three weeks the patient had seemed rather dull and dazed in general reaction. He did not respond as quickly to conversation or external happenings as before. His conversation became disjointed and although intelligable nevertheless changed from its ordinary type. For the same period his personality had changed. Instead of being considerate and kind to his wife he was irritable and touchy. His habits had become slack and careless. He was inclined not to bother about shaving and washing and tended to sleep excessively during day and night. The headache, which had been present during the "influenzal" attack, disappeared but had reappeared in the last week. It was constant, very severe and seemed to encircle the head. Weakness of the left hand developed abruptly one day and since then it had been too weak for ordinary use. His wife also noticed that he did not lift the left leg well on going upstairs. She remarked that he was more talkative than he used to be. As long as he could remember (eight years) he had been inclined to fall asleep easily. He had put on about 2½ stones in weight in the winter of 1938.

Examination (positive findings only).—Loquacious, prepared to discourse at length on any subject, e.g. V.D., marriage; gave a rambling account of his illness. V.A.R. 6/9. V.A.L. 6/6. Right fundus (fig. 14) showed numerous abnormal vessels in which it was impossible to tell arteries from veins. Left fundus normal. Right inferior and internal rectus weakness causing diplopia. Left lower facial weakness, most marked on emotional movement. Vestibular and cochlear functions normal. Some weakness of left sternomastoid and trapezius muscles. Left shoulder held at a lower level than right. Some falling away of the left arm, forearm and hand. General diminution in strength of all muscles of left upper and lower limb, especially dorsiflexion. Slight spasticity of left leg. Co-ordination normal.

Reflexes: Left abdominals diminished. Right: knee jerk ±; ankle-jerk ±; plantars ? Left: knee jerk +; ankle-jerk +; plantar ↑

Sensation: Normal to all forms.

Gait: Tended to drag left leg.

Heart: Normal.

Blood-pressure 130/80. No murmur over skull.

Other systems normal.

C.S.F.: Initial pressure 210 mm. No block. Straw-coloured with a little blood. Protein 0·055 grm. per cent. W.R. negative. 1 cell. Hæmobilirubin 0·5 mgm. per cent.

Case 2.—Anomalous vessels in right fundus; signs of a mid-brain lesion; mental changes; subarachnoid hæmorrhage; pigmented nævus.

Male, aged 16. Admitted to the National Hospital April 15, 1937, under the care of Dr. Critchley.

Family history.—Normal.

Present illness.—Up to six months of age frequent convulsions and a stomach disorder with sickness. Right palpebral fissure smaller than left since birth.

Nocturnal enuresis till aged 13. At 14 he had a phase of "religious mania." At 12 he had an operation for a right inguinal hernia and undescended testicles. A second operation had to be done six months later to replace the testes. He had never been well since the second operation. Formerly he had been bright and quick, but, after it, he became quiet, dull and easily depressed. Everything became too much trouble, and he became languid and lost all desire to play games. He began to have peculiar attacks. His first attack was about three years before admission and they had been more frequent in the last eighteen months, and he had now a severe one at least every few weeks. They started with a "funny" hot feeling in the head, often a noise in the ears and a feeling of giddiness and faintness. Objects became blurred and seemed to move slightly in all directions, and at times things seemed red and green. His legs felt very shaky below the knees, and he had to sit down. His face flushed and his heart beat forcibly, so that he could feel it all over the chest and even in the neck. The beat was not rapid and seemed quite regular. At the same time he sweated noticeably. He usually felt sick but rarely vomited. They lasted a few minutes and at times were relieved by sitting down. However, he felt limp, lifeless and nauseated for as long as two hours after. Only once had he fainted and was not unconscious for more than a few seconds. Between them he had minor attacks of a similar kind which occurred almost every day and sometimes several times a day. In these he felt hot and cold all over, generally weak, afraid that he might fall and trembled slightly. About a year before admission he began to have generalized headaches. His right upper lid frequently twitched. About six months before admission he began to suffer from a periodic aching pain behind and above the right eye. This occurred every day since and lasted five to fifteen minutes. It was often associated with a headache which started at the same site and passed back to the right temple and above and behind the ear. Occasionally it spread to the vertex and over to the left side. It was a dull irritating pain, coming on suddenly and gradually passing away after about fifteen minutes; it might be severe. On looking to the right he had diplopia, one object being above the other. There were occasional flashes of light before the eyes. For about six months he had often been sick after meals. The vomiting was independent of the headache and fainting attacks. Weight steady. He had slept badly for some years. He was often depressed and in tears. His mother said he was normally intelligent but had never been more than average. He often worried about himself. He could not concentrate in the past year and was rather slow-witted, everything was too much trouble and he was inclined to be more irritable. Memory normal.

Examination.—A pale, sallow, unhealthy looking, Jewish youth. Physique moderate. *Café-au-lait* patch on lower anterior left chest. Normally intelligent. Memory fair. Speech and mood normal. Polysymptomatic and introspective. Despite his age he appeared to enjoy ill-health and was not inclined to exert himself. Lacking in vigour, mental and physical.

Cranial nerves: V.A.R. 6/36. V.A.L. 6/6 (corrected). Fields full.

Left fundus: Normal.

Right fundus (Mr. Williamson-Noble) (fig. 16): Superior temporal vein dilated. Dilatation increased as it was traced peripherally. About 4DD from the disc margin was a sausage-shaped enlargement and a short distance beyond this a cluster of three small aneurysmal dilatations. Beyond this the vein passed into an arteriovenous aneurysm which was fed by the artery at its upper margin. The retina was deficient in this region. The artery also showed some enlargement. Between the aneurysm and the macula were some powdery whitish marks probably due to retinal œdema. There was some connective tissue of congenital origin over the disc.

Pupils, moderate size, equal, central, circular, regular, reacted to light, direct and consensual and on convergence. A fine very rapid, horizontal nystagmus on lateral deviation to right and left, rather more marked on looking to the left and in both cases, in the eye to which the deviation was taking place. Right palpebral fissure narrower than the left. No en- or exophthalmos. Diplopia on looking upwards due to right superior rectus paresis. Slight weakness of the left side of the face at the angle of the mouth on natural and forced movement. Palate lifted very slightly over to the left side.

Reflexes: All tendon-jerks on left very much brisker than on right. Abdominals present and equal. Plantars both flexor.

Heart: Normal. Blood-pressure 110/70. No bruit over skull.

C.S.F.: Initial pressure 150 mm. Fluid clear and colourless. No cells seen. Total protein 0·060 grm. per cent. Fluid otherwise normal.

X-ray of skull: Normal.

Operation.—Radon seeds stitched into sclera of right eye opposite aneurysm. Three months later there was less œdema in the retina and vision, which had diminished to 6/36, improved to 6/12. He was discharged from hospital May 2, 1937.

Progress.—He continued to have headaches as before but they were now situated chiefly in the left parietal region but occasionally became general and always occurred on waking. The attacks continued as before, and two years after discharge during one of these attacks he suddenly lost consciousness and remained so for thirty-six hours. He was admitted to another hospital and blood was found in the C.S.F. which was under great pressure. On recovering consciousness the right eyelid was almost completely ptosed and the left arm and leg were weak. Both pupils were large and inactive. If he opened his eye with his finger he saw double All the tendon-jerks were brisk and the plantar reflexes extensor, especially on the left. A systolic murmur was heard over both eyes. This gradually disappeared during the course of three weeks. Since that time he had had occasional attacks of diplopia. He was also subject to fits of great depression and was very irritable and tended to stutter. He was admitted to an E.M.S. hospital on October 28, 1940, when he was then found to have pupils which were large, equal but reacted very poorly to light. Convergence was impossible. The blood-pressure was 120/65. The C.S.F. contained 0·050 grm. per cent. of protein and was under normal pressure. X-ray of skull was normal. A diagnosis of "complusion neurosis" was made at this hospital.

Case 3.—Arteriovenous aneurysm of left retinal vessels; recurrent headaches followed by unconsciousness; signs of a mid-brain lesion, mental changes.

Female, aged 35.

Family history.—Patient was eldest of six siblings, all the others being alive and well.

History.—Since a child she had been liable to attacks of vomiting lasting about six hours and followed by a period of unconsciousness lasting about five minutes. There was no tongue biting, incontinence or convulsions. Eight months before admission one of these attacks was followed by severe headache, vomiting and diplopia on looking downwards and to the right. Examination at Moorfield's Eye Hospital then showed that she had a left internal rectus palsy. The diplopia lasted about seven months and it was observed during this time that she was tilting her head to the right. Five months before admission she was seized with another attack of vomiting and unconsciousness.

Examination.—V.A.R. 6/6. V.A.L. 6/9 (corrected). In the the left fundus there

was a markedly enlarged inferior temporal artery and vein communicating near the periphery. Several aneurysmal enlargements were visible on the artery (fig. 16). The left pupil was greater than the right, both reacted normally, visual fields full. The left knee-jerk was only present on reinforcement and the right tendon-jerks were much brisker than the left and both plantar reflexes were extensor. The blood-pressure was 130/90.

C.S.F.: Initial pressure 120 mm. Protein and Lange curve normal.

X-ray of skull: Normal. W.R. negative.

Two months later the headache had improved until a week before being seen again she was seized with a severe "nerve pain" all over the top of the head. She was extremely depressed and irritable, felt "no good," a trouble to everyone and continually fell into tears. The headaches continued.

When last seen in October, 1942, she continued to have attacks of unconsciousness and diplopia. The vision in the left eye remained unchanged. Examination now showed pupils that were inactive to light and on convergence. The left was larger than the right. Both were irregular. The left upper lid was slightly ptosed. Conjugate upward movement of the eyes was impossible. A left internal rectus palsy was present. There was slight ataxia of the right hand with intention tremor. All tendon-jerks were difficult to obtain. Both plantar reflexes were extensor. She was depressed and tearful. A systolic murmur was heard on the left side of the skull. Heart was enlarged to the left. Blood-pressure was 130/60.

Case 4.—Nævus of right retina; mental changes; signs of lesion of mid-brain; general signs of intracranial arteriovenous aneurysm.

Male, aged 17. Admitted to the National Hospital, November 28, 1935, under the care of Dr. Carmichael.

Family history.—Normal.

Present illness.—Six and a half years before admission he fell at school hitting his head against the concrete floor. He was dazed, but picked himself up and walked to the classroom with a bruise over the right eye. There he began to talk nonsense, "he could say all he wanted to say but he spoke about his home, his school, his games and his friends all jumbled up together." He was taken home (five minutes walk) and when he reached home he was still talking nonsense, complained of a frontal headache and vomited. That night he slept well, but next morning he was still talking nonsense and continued to do so for two more days. This gradually passed off. A week later he still was not quite normal, he lay about "not at all like his usual self," not joining in games, &c. He complained of frequent headaches on the top of his head radiating down his neck, a continuous ache all day, not associated with nausea, vomiting or visual phenomena, sometimes keeping him awake at night. Except for a period of three weeks he had had headaches ever since, coming on usually when he waked in the morning, worse on stooping and coughing or other exertion. During the whole time his legs were unsteady. If he got up quickly off a chair he staggered a little. His hands throughout were steady. He remained quiet and "not his usual self with no life in him." At school he became backward. He could never keep a job "because he was so awkward." He stumbled about all over the place. His condition remained like this until a second accident three months before admission. He rode his bicycle into the back of a car shooting himself over the handlebars. A week after this accident he suddenly saw double on looking downwards, the images being side by side. This remained. Two months before admission he was seized with sudden speech difficulty. He could only make sounds, which no one could understand. He knew just what he wanted to say, but

could not say anything. He could understand everything that was said to him and could do everything with his hands as usual. An hour later there was an onset of headache up the back of the head; he vomited twice and felt giddy. When he stood up he felt light in the head as if he was floating. There was no change in the diplopia. That night he vomited again. Next morning he woke feeling well and was able to talk again but he could not speak as quickly as usual. This slight slowness in his speech had persisted since. His memory had been rather worse since the second accident and he was restless and fidgeted continuously, even when asleep.

Examination.—A heavily-built, big-boned boy. Height 6 feet. Weight 9 st. 10 lb. Skull: big features, acromegalic in type with a large wide nose, heavy malar bones. Orbital ridges normal. No prognathism. No murmurs heard on auscultation. Circumference of skull normal. Both upper eyelids looked somewhat puffy. Hairy mole over the left side of the neck, 2 by 1½ cm. in length. Left arm 1½ cm. shorter than right. Hands large but not acromegalic in type. Left leg 3 cm. shorter than right. Feet normal. Quiet and alert. Co-operative. Well orientated. His memory and intelligence were definitely impaired. He himself gave a history full of mistakes as far as dates were concerned, as far as six years out in the duration of his main symptoms. ? slight degree of dysarthria.

Cranial Nerves: V.A.R. 6/6. V.A.L. 6/6. Visual fields full. Left fundus normal. Right fundus (Mr. Williamson-Noble): far out in the upper half of the retina (about 6DD from disc) there was a small dark red oval area about a quarter the size of the disc. It lay alongside a vessel. It was diffusely pigmented and the choroid vessels showed clearly in this area. It was of the nature of a nævus. No true ptosis but both palprebral fissures narrowed. Pupils: Left not quite circular, slightly larger than right; both central. Both reacted briskly and fully to light (direct and consensual) and on convergence. No diplopia. Convergence full. Outward ocular movements full, with a few ill-sustained nystagmoid jerks to right and left.

Gait: Natural, but slightly unsteady when turning quickly.

Reflexes: All tendon-jerks in arms very sluggish. Abdominals present and equal. Plantars equivocal. Tendon-jerks in legs normal.

Sensation: Normal.

C.S.F.: Pressure—240 mm. Clear and colourless. Cells 1 per cm. Protein 0·075 grm. per cent. Lange, no change. W.R. negative in C.S.F. and blood.

X-ray of skull: Normal.

Ventriculography showed a marked filling defect in the floor of the 3rd ventricle. The ventricular fluid showed no abnormality on either side. It was clear and colourless and contained less than 0·01 grm. per cent. of protein. He was very drowsy after ventriculography for about a month and vomited occasionally. The pulse ran usually about 60-70 but dropped at times to 56-58 per minute. He complained also of a constant headache on the top of his head. He did not co-operate well in examination, as he continually wanted to go to sleep, and for this reason resented being awakened and made to do things. He was very ataxic.

Progress.—Some seven months after admission he was still very ataxic and just able to walk alone. He still had severe occipital and frontal headache, but only occasional drowsiness. He was putting on weight very rapidly. The pupils now were inactive to light and on convergence. Eighteen months after admission he had put on about 2½ st. in weight, but remained otherwise with the same symptoms as before.

Examination now showed the fundi as before. Pupils 6 mm. in diameter. Both slightly irregular in outline. Reactions to direct and consensual light prompt but

of small range and poorly held. Reaction on convergence prompt, full and well held. An unusual fullness of the eyelids, which produced a bilateral ptosis, more marked on the left, where in addition arterial pusation could be seen. This pulsation was hardly palpable. Slight left proptosis. Facial asymmetry from weakness of the left lower face, in both emotional and voluntary movements. Taste not appreciated over the right anterior two-thirds of the tongue. A loud bruit, synchronous with systole, heard over both eyes, over the temples and behind the ears. Equally loud on both sides. Carotid compression abolished the ipsilateral bruit but left the contralateral unaffected. Occipital artery slightly enlarged on both sides. A suggestion of hypotonicity in the left arm. Slight inco-ordination in the finger-nose test, more marked on left. Very slight hypotonicity of the left leg.

Reflexes: As before, but now right abdominals brisker than left. Slight enlargement of the heart to the left, the apex beat being just outside the nipple line (5¼ in. from the mid-line). An apical thrill was present. Impurity of the second sound at the aortic area and near the inner ends of the right costal cartilages a faint diastolic murmur was audible. Radial pulses equal in volume. Blood-pressure right 100/45, left 105/50.

Treated by a course of deep X-ray therapy with slight improvement and some relief of headache.

Case 5.—Arteriovenous aneurysm of right retina; recurrent signs of a mid-brain lesion; later signs of intracranial arteriovenous aneurysm.

Female, aged 29, in 1926.

Family and past history.—Normal.

Present illness.—At 21 years the vision of the right eye was found to be poor and she began to suffer from recurrent occipital headache at long intervals. They came on suddenly, were very severe and associated with stiffness of the neck, nausea and vomiting. They lasted two to three days. In one of them she had diplopia and it was noted that the right eye looked outwards and its lid drooped. In the course of the next three weeks the symptoms disappeared. She had an exactly similar attack about fourteen months later, and, following this, noticed that the vision of the right eye had considerably deteriorated. She again made a good recovery from the attack but remained extremely depressed, listless, tearful and polysymptomatic. At 25, the sight was found to have improved considerably in the affected eye. At 27, she was suddenly seized with intense headache and lost consciousness for two hours. On recovery there was stiffness of the neck, a positive Kernig's sign, a divergent squint of the right eye, partial bilateral ptosis, both pupils were inactive to light, there was an almost complete left hemiplegia and speech was hesitant and slurred. She recovered rapidly in the course of a week but was left with a constant diplopia on looking to the left and upwards. Visual acuity in the right eye 6/18 and left 6/6 with glasses. She remained well until the age of 29, when in June, 1926, she began to suffer from a severe occipital headache, nausea and vomiting on waking in the morning. She was admitted to a private nursing home on January 23, 1927, and was found to have the following physical signs: the left-pupil was larger than the right, both were inactive to light and on convergence; bilateral ptosis, right more than left; divergent strabismus of the right eye; slight proptosis of the right eye; visual acuity 6/18 right, 6/6 left (corrected). In the left fundus the disc was highly coloured and the edges blurred, otherwise there was a remarkable condition, which is well shown in the painting (fig. 17). The disc had a blurred edge and, emerging from its centre and running downwards was an artery with a large spindle-shaped dilatation at its beginning. Passing laterally

from the disc was another widened artery, which apparently turned downwards just before reaching the macular region, where it became widely dilated and there was a small spindle-shaped aneurysm on it. It was difficult to distinguish arteries from veins. Above the disc were several large tortuous vessels beginning and ending suddenly and apparently communicating with the choroidal vessels. There was weakness of the left lower face, intention tremor and ataxia in the right arm and some weakness in the grip of the left hand and in dorsiflexion of the left foot. All tendon-jerks on the left side were increased and on the left side the abdominals were absent and both plantar responses were extensor. Diminution to all forms of superficial and deep sensation on the left side of the body.

X-ray of skull: Normal.

C.S.F.: Pressure—280. Protein 0·080 grm. per cent.

The patient improved gradually and the blurring of the disc edges gradually subsided. The proptosis disappeared. The weakness of the left side improved, but the ataxia of the right arm diplopia and partial bilateral ptosis remained. A year later she began to complain of tinnitus in the right ear and it was then found that on auscultation a murmur, synchronous with the heart beat, was present over the right side of the occipital region and there were dilatations of blood-vessels of the scalp and increased pulsation of the carotid artery on the right side. Slight proptosis of the right eye now re-appeared. She was last seen in 1927 and further inquiries have failed to trace her.

Case 6.—Arteriovenous aneurysm of right retina; recurrent signs of mid-brain lesion; appearance of signs of intracranial arteriovenous aneurysm.

Male, aged 18. Admitted to the National Hospital November 20, 1924, under the care of Dr. Risien Russell.

Family history.—Nil relevant.

History.—At 14 he developed poliomyelitis in the right lower limb. Little recovery of function occurred afterwards. At that time it was noted that visual acuity was 6/20 right, 6/5 left. About two weeks before admission, when walking in the street his vision gradually became blurred and after a quarter of an hour the defect was at its worst. He could see to go home. The sight was blurred all over the field of vision making it impossible to read. At the same time he felt a dull pain at the back of the head on the right side, and was very sleepy. The headache was gone the next day and the lethargy did not last longer than a few hours. The vision had gradually improved since and on admission there was merely mistiness of distant vision. Since the vision had improved he had seen double however.

Examination.—Right fundus (fig. 18): vessels extremely tortuous and greatly engorged, especially in the neighbourhood of the disc. Arteries and veins approximate in calibre, both being greatly increased in size. The superior temporal vessels were very tortuous looping backwards on themselves and a direct communication between artery and vein was present. There was a loop of hæmorrhoidal-like superior nasal vessels folded back over the disc which on closer examination were seen to be an enlarged artery and vein in direct communication. Slightly to the temporal side was a small patch of retinal pigment disturbance. Below the disc a large vessel communicated with the choroidal circulation. The outer half of the disc itself was a little pale, but within physiological limits. Visual acuity, right 6/60, left 6/6. Pupils, left slightly larger than right, central, circular, regular, reacted to light, consensual and direct and on convergence. Palpebral fissures equal. Convergence present but not sustained in right eye. Slight conjunctival injection in both eyes. Crossed diplopia on looking to left and upwards; right 3rd nerve paresis. Tone in

arms normal, proximally and distally. Co-ordination accurate, intention tremor at end of movement in both arms. All muscles of right leg wasted, especially the thigh muscles (old poliomyelitis). Right foot in attitude of pes cavus, blue and cold. Tone normal left, diminished right. Co-ordination normal left, impossible right. Power—left normal, right unable to lift whole leg from the bed, but able to extend hip joint fairly well. Adduction and abduction impossible. Flexion of knee fair. Extension weak. Very feeble dorsiflexion of foot, feeble extension. Tendon-jerks in left are brisker than right, absent in right leg. Left abdominals diminished. Both plantars flexor.

Progress.—He improved considerably and visual acuity was 6/24 on discharge one month later. Two years later he was again seized with a similar attack of mistiness of the right eye, severe occipital headache and vomiting, ptosis of both eyes and tinnitus in the right ear. Examination now showed rigidity of neck, and visual acuity in the right eye reduced to finger counting. The fundus was as before except that the disc was now definitely paler than normal. The left eye was normal. Bilateral partial ptosis, right greater than left. Right eye looked downwards and outwards and could not be moved upwards or inwards. Left eye would not move upwards and nystagmus was present in this eye on lateral deviation to either side. Right eye slightly proptosed. Pupils, right greater than left, both irregular. Reacted very poorly to both light and attempted convergence. Both upper limbs hypotonic, left greater than right with intention tremor and ataxia of movement. Left arm weak in all movements. Right leg as before. Left leg hypotonic, ataxic and dorsiflexion weak. Speech slightly dysarthric. Tendon reflexes in both arms diminished, but left brisker than right. Left abdominals absent. Left plantar extensor. Sensation normal. Blood-pressure 110/60. C.S.F. pressure over 300 mm. Fluid pink. Red blood corpuscles 20,000 per cu. mm. Protein 0·100 grm. per cent. His condition improved in that the vomiting ceased and his left limbs improved in strength. The ptosis receded. He now complained of generalized headache and the tinnitus in the right ear became more marked, and was now synchronous with the pulse. It was now seen that the veins were dilated over the right side of the scalp particularly and there was excessive pulsation of the right carotid artery. A systolic murmur synchronous with the pulse was heard all over the head especially over both eyes and over the right ear. He was discharged unchanged.

Case 7.—Enormous hydrocephalus; "fits"; nævus of forehead; arteriovenous aneurysm of left retinal vessels; signs of mid-brain lesion; subarachnoid hæmorrhage; other congenital anomalies; autopsy.

Male, aged 32. Admitted to the National Hospital May 27, 1940, under the care of Dr. Elkington.

History.—He was born with a large head. "Milestones" normal. When aged 2 years he was first noticed to have attacks like *petit mal* in which he momentarily lost himself. His head was then found to be larger and there was a large bulge on the left parietal region and a nævus over the centre of the forehead. This latter gradually became fainter as he grew older. Up to the age of 15 he had attacks about once a month. He was able to sit down in most of the attacks as they took about a minute to come on. They started with a stiffness of the right arm, clenching of the fist and rigidity and numbness of the right arm and leg. He felt he wanted to stamp his foot and rub his arm to start the circulation. Sometimes it could be aborted in this manner. If not the whole arm went stiff, the right arm pointed forward, the eyes turned to the right side and the right face twitched somewhat. He seemed dazed. They would last about three minutes. He was free of

them from 12-15 years of age and from the age of 15 onwards they occurred at intervals of six months. One of these attacks was observed and the patient was not completely unconscious. The eyes appeared to look into the distance. There was no incontinence, indeed he asked for a urinal. There was twitching of the right hand and arm for about four minutes. During the attack he got out of bed. The attack was followed by a long period of confusion and disorientation. At school he was backward, depressed and asocial. Since the age of 18 there had been progressive deafness in the right ear with a pumping noise constantly present. Since the age of 20 the vision in the right eye had been poor, but especially so in the last eighteen months. For the last three years and especially for the last six months there had been an external strabismus of the right eye with diplopia. Nine months before admission he was taken unawares by an attack and fell and fractured his skull. He recovered completely but four months later began to complain of pains in the head, commencing behind the left ear and passing forward. They were almost continuous, of increasing severity and associated with much nausea and occasionally vomiting. In the last two months there had been some further failure of memory. He was lefthanded.

Examination.—Enormous hydrocephalic skull with bulging of the left parietal and temporal region. Nose flat. Cracked-pot sound. Brown pigmentation of the forehead. Vascular nævus on left forehead. Several large pigmented nævi over the body. Intelligence subnormal. Depressed. Quiet. Introspective. Visual acuity 6/9 right, 6/6 left. The axes of the eyes pointed downwards. The right eye at rest looked downwards and outwards. Right-sided homonymous hemianopia, bisecting the fixation point. In the left fundus was an arteriovenous aneurysm of the superior temporal artery and vein. The artery and vein were both enlarged and the artery showed a number of small aneurysms near the disc. There was a direct arteriovenous communication at the periphery. Right pupil larger than left. Both reacted extremely sluggishly to light. Convergence impossible. Gross coarse nystagmus on deviation to either side and a rotary nystagmus on attempting to look upwards. Right divergent strabismus. Conjugate upward voluntary movement of both eyes absent. If however an object was first fixed and then slowly moved upwards almost full range of conjugate upward movement was present. Slight weakness of the left lower face. Nerve deafness in both ears, right and left. Complete absence of the small muscles of the right thumb. A congenital deformity of the right index finger, which was fixed in flexion at the distal interphalangeal joint. Weakness of all movements of the left arm. Slight ataxia and intention tremor of both upper limbs in finger-nose test, with dysdiadochokinesis. Falling away of the left outstretched arm. Considerable weakness of all movements of the left leg, especially in dorsiflexion of the left ankle and extension of the knee. Considerable ataxia of both legs with intention tremor. All the tendon reflexes on the right side extremely difficult to obtain whereas they were brisk on left. Left plantar extensor. All abdominals reflexes absent. In walking tended to drag left leg and to fall to the left side.

Radiographs.—Gross hydrocephalus. An old left parietal fracture and spina bifida occulta of D 4, 5 and 6.

Lumbar puncture showed a pressure of over 300 mm. Fluid was blood-stained with yellow supernatant. Hæmobilirubin 1·1 mgm. per cent. 114 lymphocytes. 56,000 R.B.C. Protein 0·880 grm. per cent.

He died a fortnight after discharge with continuous bleeding into the C.S.F. and despite repeated lumbar puncture.

Autopsy (Mr. N. J. Duggan F.R.C.S.).—Only the barest details are available.

On opening the skull and dura, large quantities of blood were found in the subarachnoid space. There was an enormous dilatation of the third and lateral ventricles with extreme thinning of the substance of the hemispheres. An arteriovenous aneurysm was found on the dorsum of the mid-brain. It occupied both sides of this region, but more so on the left and extended deeply into the basis pedunculi particularly on the right side. The anomalous vessels extended in the left optic tract and nerve into the left retina. Only the right kidney was present. Histological examination of the affected tissue showed cross-sections of vessels of all sizes with irregular thickening of their walls and areas of gliosis and hæmorrhage within the substance of the neural tissue.

Case 8.—Hydrocephalic symptoms and signs of a mid-brain lesion; subarachnoid hæmorrhage. Autopsy revealed an arteriovenous aneurysm of the mid-brain; Meckel's diverticulum; six lumbar vertebræ.

Male, aged 19. Admitted to the National Hospital April 15, 1936, under the care of Dr. Carmichael.

Family history.—Nil relevant.

Present illness.—Four years before admission it was noticed that his face was lop-sided and the left side was weak and did not move in smiling as the right side did. One week before admission he was troubled with a vague headache, especially over the left eye and the eyelids drooped. This remained and three days later he was suddenly seized by vomiting, diarrhœa and diplopia. The next day the diarrhœa and vomiting ceased but the diplopia remained. It could, however, be avoided by careful focusing, but any sudden conjugate movement of the eyes brought it back.

Examination.—Right side of face smaller than left. Right fundus: inner edges of disc hazy and grey, no swelling. A streaky hæmorrhage present. Left fundus: similar but no hæmorrhage present. Bilateral ptosis. Right eye did not move upwards. Ill sustained, irregular nystagmus on lateral deviation. Right pupil smaller than left. Left side of face did not move as well as right in emotional movement. Arms normal. Slight dragging of the left leg with slight generalized weakness especially in dorsiflexion. Tendon-jerks in arms brisk and equal. Left abdominal reflexes diminished. Left plantar reflex extensor, right equivocal.

C.S.F. pressure over 300 mm. Fluid blood-stained. Protein content 0·075 grm. per cent.

Progress.—The patient showed gradual improvement and another lumbar puncture performed 12 days after admission showed a C.S.F. pressure of 235 mm., the fluid no longer being blood-stained. The protein content was unchanged. Ventriculography was performed and this showed the lateral ventricles to be somewhat dilated symmetrically. He continued to improve. The headache, ptosis and diplopia disappeared but three months after admission he began to have recurrence of morning headaches and sickness and examination then revealed definite papillœdema in both eyes. Diplopia was now present on looking to the left, due to a right internal rectus weakness Nystagmus was present on conjugate deviation of the eyes to the right or left. The weakness of the left side of the mouth remained. All the tendon reflexes on the left side of the body were brisker than on the right and the left plantar was extensor, the right being indeterminate.

In the next six weeks his condition gradually improved, the papillœdema subsided, but the diplopia remained. He was discharged four and half months after admission, and remained unchanged until nine and a half months after the first attack when he began to have slight difficulty with his speech. A week later on being called in the morning he was suddenly sick and rapidly became semi-

conscious. He tried to speak but his tongue seemed thick. He was limp and lay motionless and unresponsive. He was readmitted to hospital that day (January 30, 1937).

Examination.—Deeply unconscious. T. 99·6° F. P.R. 52/24. Completely flaccid. He moved the right arm and leg occasionally but not the left. No neck rigidity. Unrousable. Condition resembled a deep sleep. In both fundi there were several fresh hæmorrhages. Pupils widely dilated and fixed. Corneal reflexes present. All tendon-jerks unobtainable. Abdominal reflexes present and equal on right and left. Right plantar reflex, flexor; left extensor. Blood-pressure 165/86. Tachycardia.

C.S.F.: Fluid under high pressure and yellow with numerous red blood cells. Ventricular tapping was undertaken and pale blood-tinged fluid was obtained under very high pressure. There was much less blood than in lumbar fluid. R.B.C.—20,000. Protein 0·300 grm. per cent.

Next day he had partly recovered consciousness. He then spoke in a thick gutteral voice. Papillœdema was present. There was a complete right and a partial left ptosis. The pupils were large and fixed. Slight divergent squint of each eye with almost complete ophthalmoplegia of both except for slight outward movement of each eye, left more than right. Right corneal reflex brisk, left diminished. Complete left hemiplegia. Marked loss to all forms of sensation on the left side of the body. Both plantar reflexes extensor. Sensation normal.

He gradually regained consciousness but on the eleventh day after readmission again lost consciousness and died that day, February 10, 1937.

Autopsy (Dr. J. G. Greenfield).—Meckel's diverticulum present. Arteriovenous aneurysm over the tectum of the mid-brain, especially on the right side. Cortex thin, convolutions very flattened. Moderate cerebellar pressure cone. On raising the cerebral hemispheres from the tentorium a very large dilated vein was seen running from the pineal region into the straight sinus. This connected with a tangle of dilated veins which overlay the tectum of the mid-brain, especially on the right side. The veins elsewhere on the surface of the brain and cerebellum and the dural sinuses were distended, but not thrombosed. The right jugular bulb was particularly large and formed a deep groove in the petrous bone (the left lateral sinus received blood from the straight sinus). The basilar artery was large, as also were the vertebrals. The posterior inferior cerebellar artery came off the lower part of the basilar forming a loop over the anterior border of the cerebellum before winding round to the ventricle region. There was an extra branch coming off the upper end of the basilar on the right side just beside the posterior cerebral artery and running to the tangle of vessels on the back of the mid-brain. Considerable hydrocephalus was present, but there was no evidence of meningeal hæmorrhage. The lumbar spine curved backwards below the 5th lumbar vertebræ to a 6th vertebræ rather long and narrow and the junction between this and the sacrum formed a more obtuse angle than the usual lumbo-sacral junction.

The histological findings showed an arteriovenous aneurysm which extended into the dorsum of the mid-brain especially on the right side (figs. 19-23). The highest sections showed destruction of the medial nucleus of the right thalamus by a large hæmorrhage. Sections cut through the brain stem at the level of the mammillary bodies showed a large hæmorrhage ventrally on the right side. This had completely destroyed the pulvinar, the red nucleus, lemnisci and spino-thalamic tract on that side. Dorsal to this and separated by a portion of more or less normal tissue was the main mass of the arteriovenous aneurysm. The pyramidal tract was not obviously affected although it lay in close proximity to the hæmorrhage. Sections through the brain stem at the level of the superior colliculi showed that the

hæmorrhage was still present on the right side. It lay obliquely across the whole right half of the brain stem. Ventrally this reached almost as far as the substantia nigra and dorsally almost to the region of the aqueduct. It had completely destroyed the red nucleus, the spino-thalamic tract, lemnisci, the brachium conjunctivum, the rubrospinal tract, and the 3rd nerve nucleus. It had extended across to the left and affected the 3rd nerve nucleus there also. Dorsally and separated from the hæmorrhage by a thin lamina of nervous tissue lay the mass of the arteriovenous aneurysm. This was chiefly on the right side but also extended to the left. It completely replaced the superior corpora quadrigemina by vessels of various sizes and thickness of walls. Some resembled arteries and others veins. The walls showed irregular thickening and varying amounts of elastic tissue (figs. 22-23). At the level of the anterior medullary velum the hæmorrhage was still present on the right side, but had passed considerably more dorsally and had extended to a slight extent to the left side, ventral to the aqueduct. It had destroyed the brachium conjunctivum, rubro- and tecto- spinal and spino-thalamic tracts, medial lemniscus and descending root and tract of the 5th nerve. Dorsal to the hæmorrhage and still divided from it by a thin layer of normal tissue lay the mass of the aneurysm which was again extending over to the left side to some extent. At the level of the upper portion of the pons and cerebellum, the hæmorrhage had passed even more dorsally. It was here confined to the right side of the most dorsal part of the pons, destroying the medial lemniscus, spino-thalamic, spino-tectal and rubro-spinal tracts, the descending tract and root of the 5th nerve and the medial longitudinal bundle on that side. Dorsal to the hæmorrhage and continuous with it lay the vessels at the aneurysm and it was from one of these that the hæmorrhage had occurred. The vessels lay in the cavity of the upper part of the 4th ventricle.

Case 9.—Signs of lesion of mid-brain; abnormal vessels revealed at operation. Female, aged 51. Admitted to the National Hospital February 24, 1936, under the care of Dr. Kinnier Wilson.

History.—For many years she had been deaf in the left ear, but had no tinnitus. Four years before admission she began to feel out of sorts. She got tired easily, felt a little depressed, and seemed to lose the joy of living. Three years before admission she began to feel a little giddy when she looked to the left side and the vision of the left eye began to fail. A short time afterwards double vision appeared when she looked to the left, and ultimately on looking straight ahead. The objects were side by side. About this time the left eye began to turn in to the inner canthus and ultimately became fixed there. The diplopia and giddiness were then rather less marked. About a year before admission numbness appeared suddenly on the left side of the head and forehead. This gradually spread down the left side of the face and finally to the left side of the tongue. Her taste was not impaired. About six to seven months before admission she began to suffer from severe occipital headache and pain in the upper part of the neck. These were not constant but were frequent and almost prostrating while they lasted. They were usually worse in the morning, but unassociated with vomiting, until seven weeks before admission, when for four to five days she vomited repeatedly. She then had a pumping noise in her head while she vomited. This was more marked on one side than the other. The headaches were often either brought on or exaggerated by stooping or exertion. In addition she had had a drawing feeling behind the left eye which was becoming more marked. Six months before admission she was admitted to another hospital where the following abnormal signs were found. Very low visual acuity and narrowing of field of vision all round the left eye. Right pupil dilated and reacted to light and convergence only very sluggishly. Left pupil widely dilated and fixed.

Eye movements full on the right side, all diminished on the left side. (Supr. oblique appeared to act normally though.) Absent left corneal reflexes. Impairment of pin-prick and light touch sensation over the whole distribution of the left trigeminal area. Loss of power in left masseter. An operation was performed which "fixed" the eye "straight" but prevented her moving the eye from side to side. She still had diplopia in certain movements of her eyes. Four months before admission she noticed that the left lid was drooping; within a short time it closed the eye completely. This corrected the diplopia, but the sight in the right eye had been failing ever since. She also had transient bouts of amaurosis during which objects would disappear for a few moments at a time. Her speech had recently become thick and for some months she had occasional difficulty in swallowing. Food seemed to stick behind her breast bone. For some time she had been light headed when she sat up suddenly and recently she felt she was spinning about when she laid down in bed. For the last two or three years she had had palpitations and shortness of breath on excitement or exertion. Her feet swelled a little towards the evening.

Examination.—Somewhat slow mentally but accurately orientated and no specific intellectual defect. V.A.R. 6/9. V.A.L. 1/12. Fundi: normal. Left upper lid completely ptosed. Left eye definitely proptosed but could be pushed back into the orbit without causing pain. This eye was set a little lower in the orbit so that it looked slightly down and to the left; although all movements of the right eye were full, the left eye only moved when she was asked to look downwards and then it performed a short counter clockwise rotation, so that it looked slightly to the left and upwards (M. inf. oblique). There was no nystagmus. Right pupil normal. Left pupil slightly dilated and immobile. Marked loss to cotton wool and pin-prick in the whole of the distribution of the left 5th nerve. Left corneal reflex absent. Left masseter and temporal muscles a little wasted and weak. Jaw opened sharply to left against resistance. Jaw-jerk not elicited. A slight generalized weakness of the right lower limb. Left limb normal. Tendon reflexes in arms very brisk and equal and, in legs, right were very brisk, whilst left were normal. Right plantar extensor, left flexor. Abdominals all weak.

Heart normal. Blood-pressure 160/100.

C.S.F. pressure—210 mm. Fluid clear and colourless. Protein 0·050 grm. per cent. Completely normal otherwise.

Radiograph.—Lateral and anteroposterior views showed no abnormality but a view of the base of the skull revealed erosion of the apex of the petrous bone on both sides, more so on the left (fig. 25).

Operation (March 30, 1936) (Mr. Harvey Jackson).—A small low left temporal osteoplastic flap was reflected. When the dura which was quite slack was opened a considerable amount of subarachnoid fluid escaped. There was no flattening of the convolutions. Several of the cortical arteries, however, were unusually large and tortuous suggesting a tendency to aneurysmal malformation. The temporal lobe was elevated and the middle fossa inspected intradurally but there was no sign of tumour. A large cortical vein was divided as it entered the medial end of the petrosal sinus. A free hæmorrhage from the sinus was controlled by a muscle graft. The blood-vessels round the mid-brain were enormously dilated. The bone flap was replaced with a small decompression.

Progress.—She became very aphasic in a few days after the operation and very emotional. She took no interest in anything and was completely unco-operative. No drowsiness, vomiting or incontinence. Her physical signs remained unchanged. These symptoms gradually disappeared. She was discharged from hospital unchanged since admission. Last heard of in January, 1937, when attendances suddenly ceased. Attempts to trace her have been unsuccessful.

PLATE III.

FIG. 1.

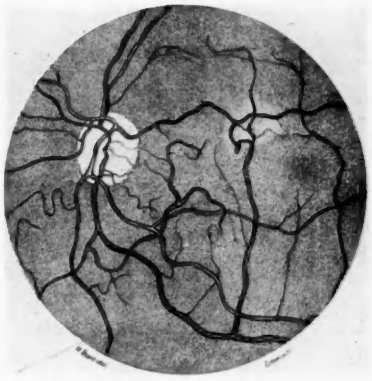

FIG. 2.

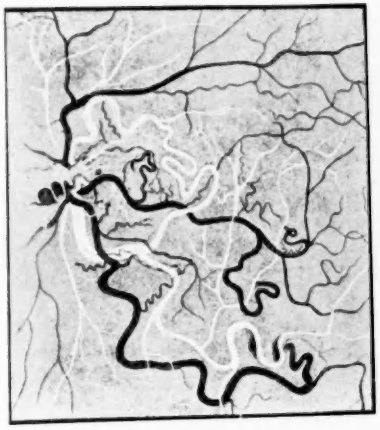

FIG. 3.

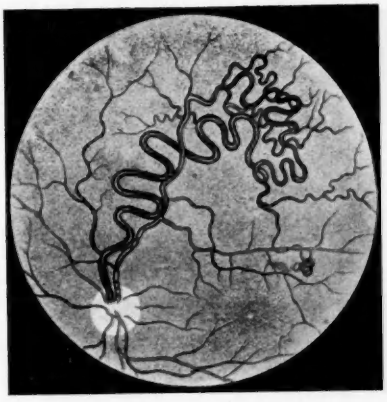

FIG. 4.

FIG. 5.

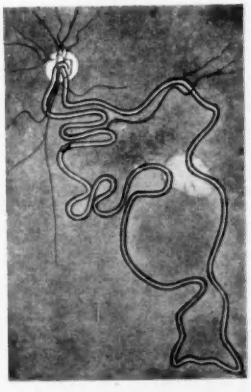

FIG. 6.

To illustrate article by Wyburn-Mason

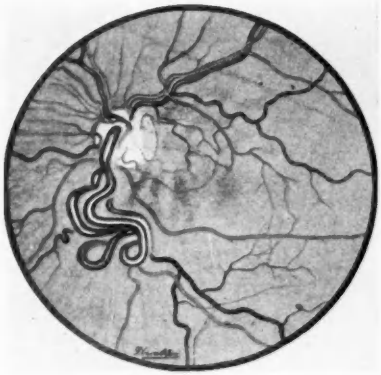

FIG. 13.

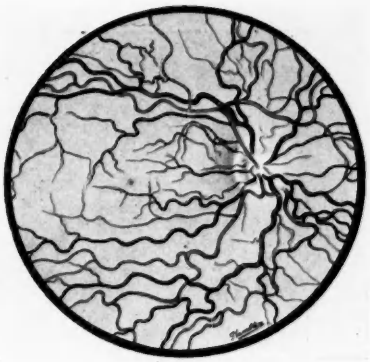

FIG. 14.

FIG. 15.

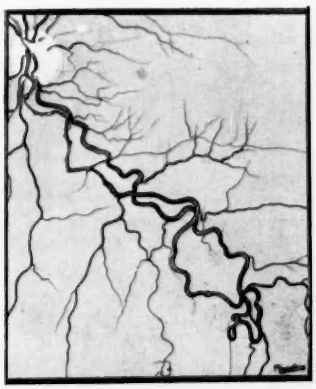

FIG. 16.

FIG. 17.

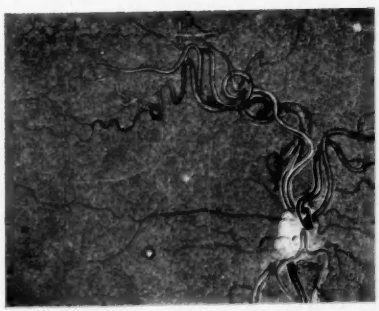

FIG. 18.

To illustrate article by Wyburn-Mason.

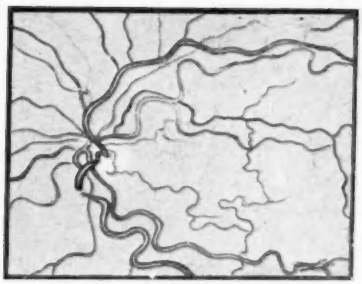

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

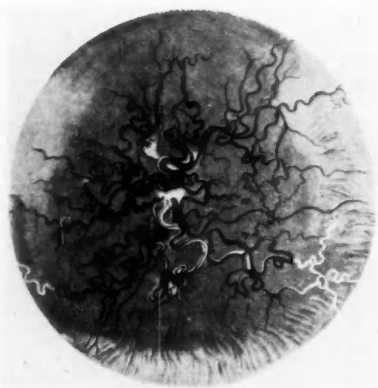

FIG. 11.

To illustrate article by Wyburn-Mason.

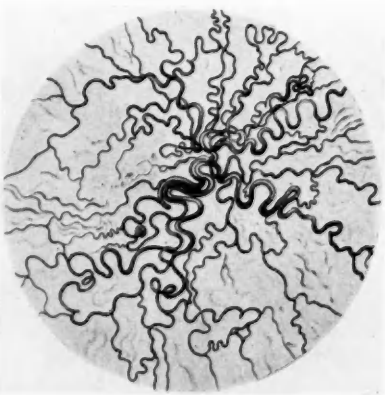

FIG. 12.

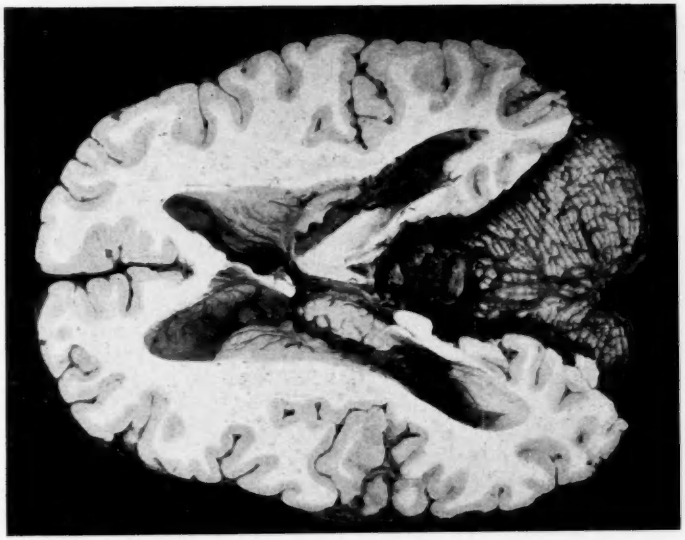

FIG. 21.

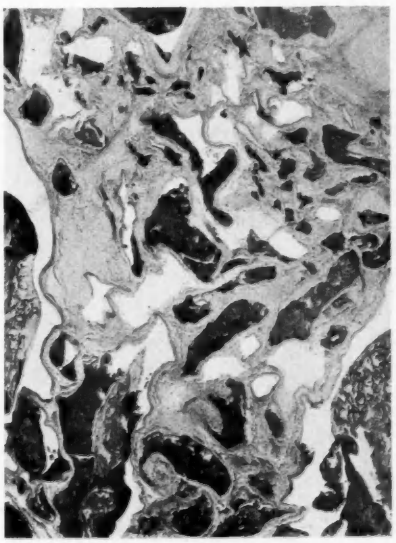

FIG. 22.

FIG. 23.

To illustrate article by Wyburn-Mason.

PLATE VI.

FIG. 19.

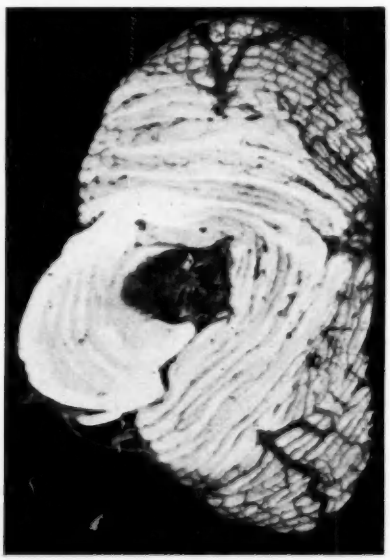

FIG. 20

To illustrate article by Wyburn-Mason.

FIG. 27.

PLATE VIII.

FIG. 25.

FIG. 26.

To illustrate article by Wyburn-Mason.

LEGENDS FOR PLATES.

PLATE III.

Fundal appearances in cases of:—

FIG. 1.—Magnus (*Virchow's Arch.*, 1874, 60).
FIG. 2.—Gunn (*Trans. Ophthal. Soc. U.K.*, 1884, 4).
FIG. 3.—Schleich (*Mitt. Ophthal. Klin. Tübingen*, 1884-90, 11).
FIG. 4.—Seydel (*Arch. Augenheilk.*, 1899, 38).
FIG. 5.—Rentz (*Arch. Augenheilk.*, 1925, 38).
FIG. 6.—Ehlers (*Acta Ophthal. Kbh.*, 1925, 2).

PLATE IV.

Fundal appearances in cases of:—

FIG. 7.—Yates and Paine (*Brain*, 1930, 52).
FIG. 8.—Brock and Dyke (*Bull. neurol. Inst. N.Y.*, 1932, 2).
FIG. 9.—Nicolato (*Ann. Ottalm.*, 1933, 61).
FIG. 10.—Stokes (*Arch. Ophthal. N.Y.*, 1934, 11).
FIG. 11.—Bonnet, Dechaume anl Blanc (*J. Méd. Lyon*, 1937, 18). Case 1.
FIG. 12.—Ditto. Case 2.

PLATE V.

FIG. 13.—Fundal appearance in Northfield's case (Guy's Hospital Reports, 1940-1, 90).
FIG. 14.—Fundal appearance in Case 1.
FIG. 15.—Fundal appearance in Case 2.
FIG. 16.—Fundal appearance in Case 3.
FIG. 17.—Fundal appearance in Case 5.
FIG. 18.—Fundal appearance in Case 6.

PLATE VI.

FIG. 19.—Coronal sections of (top left) upper part of pons, (top centre) mid-brain, and (top right) and (bottom) 3rd ventricle region showing an arteriovenous aneurysm of dorsum of mid-brain invading especially the right side of the mid-brain. A large hæmorrhagic area is present ventrally (Case 8).

FIG. 20.—Transverse section of pons and upper part of cerebellum showing extension of arteriovenous aneurysm into upper parts of 4th ventricle (Case 8).

FIG. 27.—Drawing of fundus in the late stages of a case of intracranial arteriovenous aneurysm, not located in the mid-brain.

PLATE VII.

FIG. 21.—Horizontal section through brain showing arteriovenous aneurysm of dorsum of mid-brain and hydrocephalus (Case 8).

FIG. 22.—Low-power view of vessels forming arteriovenous aneurysm of mid-brain (Case 8) showing the irregularity in the structure of the walls.

FIG. 23.—High-power view of the same vessels showing anomalous structures of walls.

PLATE VIII.

FIG. 25.—Radiograph of base of the skull in Case 9, showing erosion of apices of petrous bones.

FIG. 26.—Ventriculograph showing 3rd ventricle filling defect in Case 4.

THE VASCULAR FACTOR IN INTRACRANIAL PRESSURE AND THE MAINTENANCE OF THE CEREBROSPINAL FLUID CIRCULATION.[1]

BY JOHN E. A. O'CONNELL
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A consideration of the growth of medical knowledge reveals that progress in therapeutics frequently stimulates interest in anatomical and physiological problems. So it is that the anatomist, the physiologist and the clinician help one another and knowledge grows as a whole from the work of each of them. The development of the fields of neurology and neurosurgery has given practical interest to the study of intracranial pressure and the circulation of the cerebrospinal fluid. During the last quarter of a century much valuable research has been carried out in connection with these problems and a clear understanding has been reached on many points. Yet, in spite of these advances, it is believed that in certain respects the modern conception of intracranial pressure and the cerebrospinal fluid circulation is incomplete. The purpose of this lecture is first to review briefly the development of modern knowledge of these subjects, then to describe a series of personal observations and upon these to base a modification of views at present held as to the factors which maintain intracranial pressure and the circulation of the cerebrospinal fluid. Finally, some of the possible applications to intracranial anatomy, physiology and pathology of the observations which have been made will be considered.

Material and methods.—The observations upon which this work is based are of a simple nature. In the first place intracranial pressure has been investigated both in the cadaver and in the living patient. In the latter observations were made at lumbar, cisternal and ventricular puncture and in each case particular attention has been directed to the variations in pressure which correspond to cardiac and respiratory activity. In the second place a series of experiments have been carried out to determine the influence of the bore of the conducting tube on the transmission of pressure variations to a manometer. Simple experiments have been made to illustrate the principle of venting. Finally certain observation made during operations upon the central nervous system have been considered in their relationship with the phenomena under discussion.

[1] Hunterian lecture delivered at the Royal College of Surgeons of England on April 19, 1943.

The Modern View and its Development.

Knowledge of the cerebrospinal fluid has been gradually accumulating over a long period. The existence of the fluid had apparently been noticed by Galen in the second century. The ventricles of the brain, in which cerebrospinal fluid is produced, were well illustrated by Leonardo da Vinci over four hundred years ago. Just a hundred years ago came the publication of the work of Magendie (1842). He described the ventricles and the subarachnoid space and certain connections between them and thus demonstrated the channels in which the cerebrospinal fluid circulates. In addition he pointed out that the fluid exists at a positive pressure.

Later came knowledge of the sites of production and absorption of the fluid. In 1854 Faivre suggested that it was formed in the ventricles by the choroid plexuses. The observation by Cushing (1926) of weeping of fluid from the surface of a choroid plexus exposed at operation supported this view but proof of it came only with publication in 1919 of Dandy's brilliant experimental work. He showed that the dilatation of a lateral ventricle which normally follows occlusion of a foramen of Munro did not occur when the choroid plexus was excised from this ventricle. As regards the absorption of cerebrospinal fluid it was suggested in 1870 by Key and Retzius that it filtered out of the subarachnoid space into the venous sinuses through the pacchionian granulations. This view was confirmed and amplified by the work of Weed (1914). Although other opinions have been put forward the one just outlined concerning the sites of formation and absorption of the cerebrospinal fluid is that which is now generally accepted.

With the development of this anatomical knowledge of the choroid plexus, cerebrospinal fluid spaces and arachnoid villi there came increased physiological interest. It will now be necessary to consider briefly the views which have been held upon the mechanisms of production and absorption of the cerebrospinal fluid and the factors which have been considered responsible for its positive pressure and circulation.

While it is generally agreed that the choroid plexuses form the chief site of origin of the cerebrospinal fluid there is considerable difference of opinion as to the actual mechanism by which it is produced here. Faivre (1854) and more recently Flexner (1934) believe that it is secreted by the activity of the cells of the plexus. On the other hand Mestrezat (1912) and Fremont Smith (1927) have given strong support to the view that the fluid is a simple filtrate. It is not intended to discuss the arguments which have been put forward to support each of these views since the actual

mechanism of production has no bearing upon the matters to be discussed in this lecture.

According to Weed (1935) the absorption of cerebrospinal fluid into the venous sinuses depends upon two factors. In the first place since the fluid pressure is usually greater than that in the venous sinuses there will be a small hydrostatic pressure gradient favouring the passage of cerebrospinal fluid through the villi into the veins. Of greater importance is the second factor—the osmotic pressure of the proteins of the blood. This will exert a strong effect in drawing the almost protein-free cerebrospinal fluid through the villous endothelium into the venous system. According to Weed's calculations the hydrostatic factor is but 15 to 35 mm. of fluid in four-footed animals whereas the osmotic one amounts to 250 to 300 mm. of fluid.

Next must be considered the factors which have been held responsible for the normal positive intracranial tension. Weed (1929) believes that the pressure of the cerebrospinal fluid is to be considered as an independent pressure of a body fluid and that it represents the balance between the processes of production and absorption. He believes that the elasticity of the dura is unimportant in the maintenance of the normal pressure and states that hydrostatic factors are important only in positions other than the horizontal. As regards the relationship of cerebrospinal fluid pressure to intracranial intravascular pressures he believes that the arterial pressure has little bearing on the cerebrospinal fluid pressure but that the venous pressure is more closely related. Howe (1929) suggests that normal cerebrospinal fluid pressure is maintained by the secretion of sufficient fluid to moderately distend the dura. Solomon (1929) states that the pressure tends to be constant for the individual and believes that there is a mechanism which maintains the pressure in a state of equilibrium. As factors in the maintenance of this equilibrium he suggests the amount of blood in the head, the balance between secretion and absorption of the cerebrospinal fluid and the elasticity of the spinal dural sac. Again Fremont Smith and Kubie (1929) state that the volume and pressure of the cerebrospinal fluid are maintained by a delicately balanced osmotic and hydrostatic equilibrium between the cerebrospinal fluid and the blood. It will therefore be seen that the opinion is widely accepted that the normal positive pressure of the cerebrospinal fluid is due to the balance which exists between the rates of its production and absorption.

Finally in this review some mention must be made of the modern view concerning the forces responsible for the circulation of the cerebrospinal fluid. There is difference of opinion on the rate at which the cerebrospinal

fluid is formed and absorbed. On the one hand there are the observations of Dandy and Blackfan (1914) upon the rate of absorption of dye from the subarachnoid space. These suggest that in the adult between 500 and 800 c.c. of fluid are produced and absorbed in twenty-four hours. In support of this view is the fact that in the presence of a cerebrospinal fluid leak a large volume of fluid can be collected in twenty-four hours: against this later point it has been argued that conditions are abnormal in the presence of such a leak. On the other hand there are those who believe that the rate of production of cerebrospinal fluid is very much slower than the above observations suggest. Flexner and Winters (1932), from observations upon cats, conclude that in these animals under anæsthesia only 9 to 16 c.c. of fluid is formed in twenty-four hours. Although the authors pointed out that the volume of fluid formed was independent of the size of the animal's brain (within the limits of their experiments), it seems worthy of note that the cat's brain weighs less than one-fiftieth of that of an adult man. It would not be surprising if the volume of fluid formed in man in a given period were as much as fifty times the volume formed in a cat (i.e. over 500 c.c. in twenty-four hours). It may further be pointed out that in the experiments of Flexner and Winters the possible influence of the absorptive mechanism on the production of fluid was removed. Although it will be seen that from the evidence available there is considerable doubt as to the normal rate of cerebrospinal fluid production it appears to be accepted by many that there is but a slow passage of fluid through the subarachnoid space from the choroid plexus to the arachnoid villi and that the movement is determined by the forces of production and absorption. Howe (1929) supports this view and as arguments in favour of it points out that since its function is purely mechanical a rapid circulation of the fluid would serve no purpose: again, its constitution varies in different localities which would not be expected if the circulation were a rapid one: and finally he states that foreign particles injected into the subarachnoid space diffuse slowly and unequally. He points out that some have supposed that the cerebral pulsations might favour the circulation of the cerebrospinal fluid but believes that these pulsations are extremely slight (2 to 3 mm. of fluid at lumbar puncture) and therefore of little physiological importance in effecting the circulation. Again Fremont Smith and Kubie (1929) point out that the pressure variations with cardiac activity amount only to 2 to 4 mm. of cerebrospinal fluid and with respiratory activity to 5 to 10 mm. Little importance has therefore been attached to the variations in cerebrospinal fluid pressure which occur with cardiac and respiratory activity. Greenfield and Carmichael (1925) do however

point to the waves superimposed by this activity upon the steady tide of circulation between the points of production and absorption of the fluid. They suggest that the replacement of fluid in the spinal canal is due to the pulsations induced by cardiac and respiratory activity.

This review of what is believed to be the modern point of view may now be briefly summarized. First it is widely accepted that the normal positive intracranial pressure is due to the balance existing between the processes of production and absorption of the cerebrospinal fluid. Secondly, most observers have considered that during a given period of observation the cerebrospinal fluid pressure is relatively constant and subject to but slight and unimportant variation with cardiac and respiratory activity. Thirdly it is accepted that the circulation of the fluid is a movement from its point of production towards the arachnoid villi to replace fluid which has been absorbed in this situation. And finally although arguments may be adduced to the contrary it is accepted by many that the circulation of the cerebrospinal fluid is a slow process.

Personal Observations.

In a number of instances lumbar and cisternal punctures have been performed on the cadaver at a varying period after death. It was found that when the procedure was carried out in the horizontal position the pressure was not greater than that of the atmosphere in any case. As a result no fluid dripped from the needle and no manometric recording could be made. What is the cause of this fall in cerebrospinal fluid pressure after death? It is believed that when the blood ceases to circulate the formation and absorption of cerebrospinal fluid also cease, and that for this reason a diminution of the volume of cerebrospinal fluid present cannot occur. If, as is believed to be the case, the volume of the cerebrospinal fluid is unaltered after death then the fall in its pressure which has been observed to occur at this time can only be accounted for by an increase in the volume of the cerebrospinal spaces. It is believed that such a change does occur and that it is due to diminution in size of intracranial blood vessels. It is clear that as the blood-pressure falls, the volume of the arterial tree diminishes. In the same way when blood fails to reach them the intracranial veins will collapse. In so far as intracranial blood volume and that of the vessels which contain this blood diminish, so will the volume of the ventricles and subarachnoid space increase, and the pressure of fluid in these spaces decrease. This then is the first of the observations which have been made pointing to the importance of a vascular factor in the maintenance of the normal positive intracranial pressure.

The second series of observations deals with cerebrospinal fluid pressure during life. In all patients in whom lumbar, cisternal or ventricular puncture has been carried out the cerebrospinal fluid pressure has been recorded—a procedure which is widely practised. Of greater value from the point of view of the present study is a record of the variations to be observed in this pressure with cardiac and respiratory activity. Such a record has been made in all cases investigated during a period of some eighteen months.

When lumbar puncture is carried out in the horizontal position in normal individuals manometric observation shows that there is a wide range of normal pressures. It is usually accepted that pressures of between 80 and 180 mm. of fluid may be considered normal. The variations in the pressure corresponding to cardiac and respiratory activity differ but slightly from case to case however. The cardiac variation may be more than 1 mm. with each heart beat; it is usually less and quite frequently is less than 0·5 mm. The respiratory variation is of course slower and may be of greater amplitude than the cardiac. Sometimes it has amounted to 2 mm. or more. In a number of cases the respiratory variation has seemed to be no greater than that occurring with cardiac activity.

Observation of cerebrospinal fluid pressure during cisternal puncture in the horizontal position reveals a wide range of normal pressures. Indeed the pressure here would be expected to be identical with that in the lumbar theca when the patient is truly horizontal. The recorded pressure variations in the cisterna magna with cardiac and respiratory activity have likewise been identical with those observed in the lumbar theca.

The observations made during ventricular puncture are of considerable interest. In the first place it must be pointed out that during this investigation ventricular puncture has been done with the intention of injecting oxygen into the ventricles for ventriculography. For this procedure the head has been raised to permit of the simultaneous tapping of both lateral ventricles in the occipital region. In this position intraventricular pressure will be lowered and will therefore not be comparable with lumbar and cisternal pressures recorded in the horizontal position. But the variations recorded in intraventricular pressure with cardiac and repiratory activity are comparable with those observed in the lumbar theca and cisterna magna and differ markedly from them. The variation of intraventricular pressure with cardiac activity has been found to lie between 5 and 50 mm. of fluid, the average variation being 15 mm. With each respiration the pressure varied from 15 to 60 mm., the average variation being 35 mm. It will be appreciated therefore that far from being constant

for the individual in a given position intraventricular pressure is subject to recurring variations, estimated by the methods used in the present series of observations, at between 20 and 110 mm. of fluid—the average figure being about 50 mm. of fluid.

It now becomes necessary to explain why the cardiac and respiratory variations in pressure are so large in the lateral ventricles and relatively so small in the subarachnoid space of the lumbar and cisternal regions. Several possible explanations suggested themselves, but it eventually became clear that the difference was purely artificial and depended on the system employed to record the pressure variations. The following series of observations demonstrates this point clearly.

For the observations upon cerebrospinal fluid pressure which have been described a lumbar puncture needle of Greenfield's pattern and Frazier's type of ventricular cannula have been employed. A similar standpipe manometer and rubber connection were employed throughout. The lumbar puncture needle has an internal diameter of less than 1 mm. and the cross sectional area of its lumen is less than 0·8 sq. mm. The ventricular cannula has an internal diameter of 2 mm. and its lumen a cross sectional area of over 3 sq. mm. The resistance offered to the flow of fluid through the small lumbar puncture needle will be greater and the rate of such flow slower than in the case of the ventricular cannula. An unchanging pressure may be more or less accurately recorded by a system making use of either needle or cannula but pressure variations will be less well transmitted through the lumbar puncture needle. If the pressure variations are rapid—even though they be considerable—they may not be recorded at all with the lumbar puncture needle. The more rapid flow of fluid through the ventricular cannula allows of better observation of pressure variations, but here too the cannula is the most resistant part of the system to the passage of fluid. Consequently it is considered that the variations in intraventricular pressure recorded with this instrument are smaller than the actual variations occurring within the ventricles.

The accuracy of these statements has been established by the following experiments. In the figure (fig. 1) there is represented an apparatus by means of which pressure variations can be set up in a length of rubber pressure tubing. The tubing is connected at one end to a reservoir of water which is supported beside a millimetre scale. Pressure variations of any desired magnitude and at any desired rate may be set up in the rubber tubing by varying the height of the reservoir to which it is connected. At its other end the tubing is connected to an ordinary standpipe manometer graduated in millimetres. The pressure tubing has an internal diameter of

5 mm. and it can be connected directly to the manometer, or the ventricular cannula or lumbar puncture needle can be introduced into the system at this point.

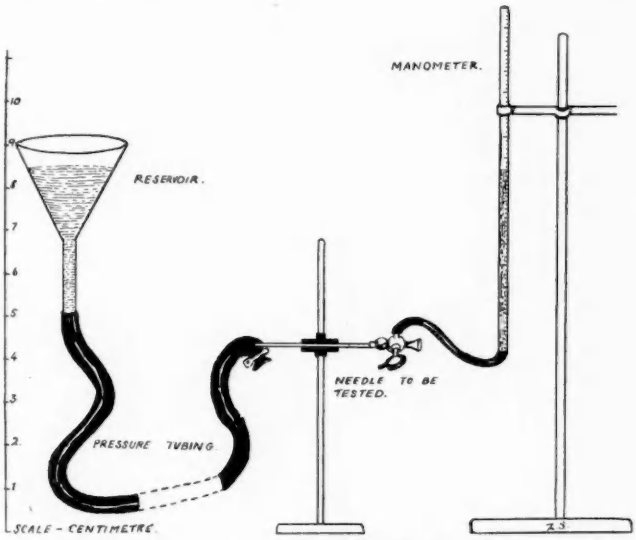

FIG. 1.—Diagram of apparatus used to demonstrate the influence of the system employed when measuring pressure variations.

The results of a series of observations made with this apparatus are shown in the table (fig. 2). From this it will be seen that the manometric

Shift or reservoir	*Rate of shift*	*Manometric variation*		
		Wide bore tubing	*Ventricular cannula*	*Lumbar puncture needle*
10 mm.	20 per minute	10 mm.	1 mm.	1 mm.
	80 per minute	10 mm.	4 mm.	1 mm.
100 mm.	20 per minute	100 mm.	100 mm.	2-3 mm.
	80 per minute	80 mm.	50 mm.	1 mm.

FIG. 2.—Table indicating the results of a series of observations upon the influence of the conducting system on the transmission of pressure variations to a manometer.

variation corresponding to a given variation in the height of the reservoir is markedly influenced by the size of the lumen of the tube through which the variations are transmitted to the manometer. Thus if the pressure

tubing is directly connected to the manometer a movement of the reservoir of 10 mm. at any rate produces a corresponding movement of the manometric level. When the excursion of the reservoir is through the 100 mm. and is a slow one the manometric level also moves through 100 mm. But if this larger reservoir excursion is a rapid one (80 times per minute) the manometric variation will no longer give a true indication of the variation in the reservoir level, e.g. 80 mm. instead of 100 mm. Thus, even pressure tubing with an internal diameter of 5 mm. presents a resistance to the rapid flow of fluid to and from the manometer. As a result of this resistance rapid pressure variations in the system are inadequately recorded on the manometer.

When the ventricular cannula is introduced between the pressure tubing and the manometer the resistance to the flow of fluid from one to the other becomes much greater. It is found that a slow variation of the level of the reservoir through 10 mm. produces a manometric variation of 7 mm., while a rapid reservoir variation of 10 mm. results in a manometric variation of only 4 mm. In the case of larger variations it is found that a slow reservoir excursion of 100 mm. produces a manometric variation of equal or nearly equal magnitude, but when this reservoir excursion of 100 mm. is rapid the manometric variation is but 40 to 50 mm.

Finally, when these observations are repeated with the lumbar puncture needle introduced between pressure tubing and manometer it becomes clear that the resistance to the passage of fluid from one to the other has still further increased. When reservoir variations of 10 mm. are made slowly the manometric variation is only 1 to 2 mm.; when they are made rapidly the manometric variation becomes less than 1 mm. When the reservoir variations of 100 mm. are made very slowly (2 to 3 excursions per minute) the manometric variation may amount to 90 mm. When made at the rate of 20 per minute the manometric variation is but 2 to 3 mm. and at a rate of 80 per minute the excursion of the manometric lever is but 1 mm. around a mean position.

To summarize these observations it may be pointed out that when pressure variations in a fluid system are under consideration the diameter of the tubing through which the variations have to be transmitted to allow of their being measured is of considerable importance. Steady pressures or slowly recurring pressure variations may be accurately recorded even when the diameter of this tubing is small (e.g. 1 mm.). However, the greater the rate of pressure variation in the system and the smaller the diameter of the connecting tubing the smaller will be the pressure variation on the manometer resulting from a given pressure change in the system. It will be

seen from this that the opinion—which is widely held—that cerebrospinal fluid pressure is subject to but slight and unimportant variations is erroneous. The opinion has probably been based on the pressure variations observed in man and animals when using needles of narrow bore. Little detail of the type of needle used during animal experiments is available but it has almost certainly not been larger than a lumbar puncture needle of the type described above. For this reason the observations made upon pressure variations during such experiments have been misleading. When making use of a ventricular cannula of the type here described a more accurate impression of the magnitude of the variations in cerebrospinal fluid pressure with cardiac and respiratory activity will be gained. But it is strongly suggested by the experiments which have been described that the variations observed with this cannula are smaller than the actual variations in cerebrospinal fluid pressure occurring within the ventricles. From calculations based on these experiments it is thought that the variations in cerebrospinal fluid pressure with both respiratory and cardiac activity are of similar magnitude, each lying between 20 and 60 mm. of fluid. This means that in an adult at rest cerebrospinal fluid pressure far from being constant varies rhythmically and through an average of about 80 mm. every three or four seconds.

During the course of operations upon the central nervous system observations may be made which support the belief expressed above that cerebrospinal fluid pressure is subject to recurring and considerable variations. The force with which the cerebrum and overlying dura are elevated at each cardiac contraction must often have been remarked upon in the course of craniotomies. Again, if during such an operation a large subarachnoid channel is pricked a jet of cerebrospinal fluid will frequently escape and the height of the jet will vary considerably with cardiac and respiratory activity. The escape of fluid when the spinal subarachnoid space is opened in the course of a laminectomy has a similar pulsatile character. These operative observations suggest that the cerebrospinal fluid pressure varies markedly with cardiac and respiratory activity and have been at variance with lumbar puncture observations. As has been seen they give a truer indication of the actual state of affairs than does lumbar puncture.

The effect of postural alteration upon cerebrospinal fluid pressure will now be considered. A simple experiment to illustrate a fundamental point must first be described (fig. 3). If a rigid cylinder full of fluid is connected to a manometer and its level is varied no variation in manometric fluid level will occur. If now the cylinder is provided with a vent, variations in its

level will produce corresponding variations in the manometric reading: in this case the fluid surfaces in both manometer and cylinder are at atmospheric pressure and therefore remain at the same horizontal level.

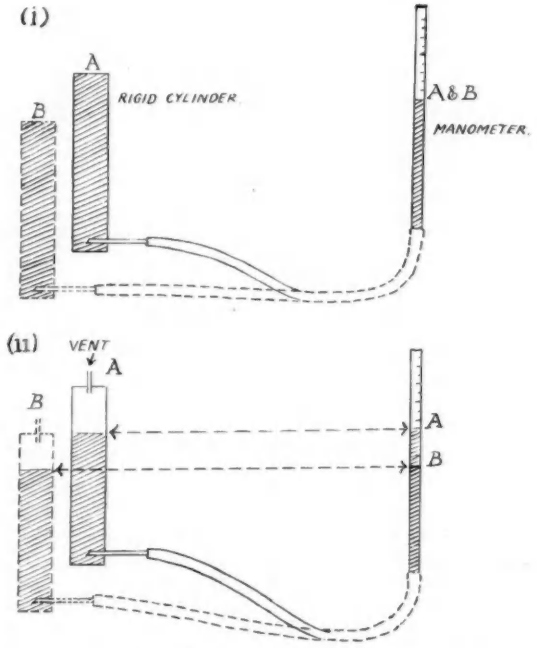

FIG. 3.—Apparatus used to demonstrate the principle of venting: (i) unvented cylinder variation in the level of which produces no alteration in manometric level: (ii) vented cylinder every variation in the level of which is accompanied by a corresponding variation in the manometric level.

When one considers the variations in cerebrospinal fluid pressure which occur with alteration of posture one is forced at once to the conclusion that the subarachnoid space is vented. Thus the pressure registered when lumbar puncture is carried out in the horizontal position will frequently be in the neighbourhood of 120 mm. of fluid. If the head end of the couch is lowered the lumbar pressure will fall. As the head end is raised the lumbar pressure will rise so that when the vertical position is reached it is between 400 and 500 mm. or even more. (These observations were made under anæsthesia with sodium pentothal.) The exact figure will depend on the distance between the lumbar puncture needle and the vertex—i.e.

height of the patient. It will usually be found (fig. 4) that when the patient's neck is flexed the level of the fluid in the manometer will be a short distance below the external occipital protuberance and when the head is fully extended the level will rise some centimetres until it is at or above the level of the protuberance. The average variation observed following such movement of the head during a series of encephalographies was 70 mm. It is clear therefore that there is venting of the subarachnoid space. What is its mechanism? It is generally believed that it is brought about

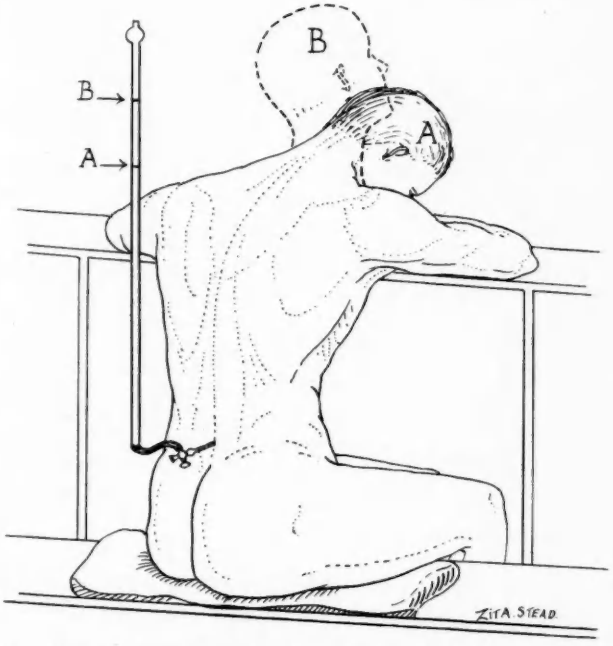

FIG. 4.—Drawing to illustrate the rise in cerebrospinal fluid pressure which occurs when the flexed head (A) is extended (B).

through the vascular system. When the head is elevated cerebrospinal fluid passes into the spinal theca and the pressure here rises, blood being retained in the cranium—especially probably in the venous bed—to take the place of the cerebrospinal fluid which has been displaced downwards. When the head is lowered cerebrospinal fluid passes into the cranium and the venting here disappears. Such collapse of the spinal subarachnoid space as occurs will be permitted by a vent here—dilatation of the spinal

extradural veins. Weed (1927) has carried out a series of very careful observations upon the effect of posture upon the cerebrospinal fluid pressure in animals. He shows that the venting is incomplete and in this way the nervous tissues are to some extent protected against great alterations in cerebrospinal fluid pressure. The observations described above upon the postural changes in cerebrospinal fluid pressure in man have in the past been made by numerous observers. They are described here only because of their bearing on the discussion to follow.

Normal Intracranial Pressure.

Cerebrospinal fluid pressure is normally estimated in the horizontal position. It may vary between 80 and 180 mm. of fluid and is not infrequently about 120 mm. It has already been seen that this normal pressure has been considered to depend upon the balance between the processes of production and absorption. From a consideration of the observations which have been described it is believed that this view is inadequate. Further it is believed that hydrostatic and vascular factors play an important part in the maintenance of the normal positive cerebrospinal fluid pressure.

When a patient is in the correct position for lumbar puncture the line of his vertebral spines will be exactly horizontal and the external occipital protuberance will be level with them—no rotation of the head being present (fig. 5). In this position it is clear that the subarachnoid space over

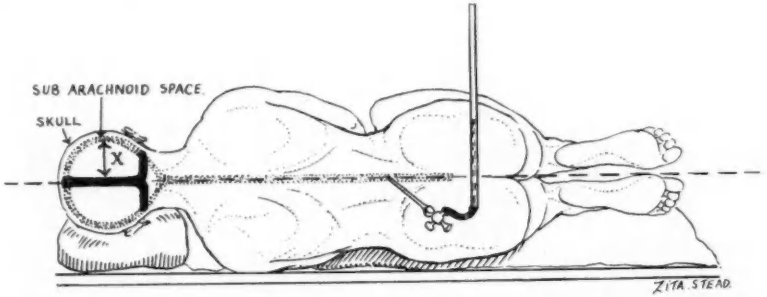

Fig. 5.—Drawing to indicate that when lumbar puncture is done in the true horizontal position there is a column of cerebrospinal fluid (X) within the skull which is entirely above the horizontal plane.

the uppermost cerebral hemisphere is entirely above the horizontal plane. The height of the resulting column of cerebrospinal fluid may be calculated by halving the maximum diameter of the head after making due allowance for the thickness of cranium and scalp. This calculation was made in

a series of adult patients and gave a result of approximately 5 cm. From this it is believed that in the average adult there is a hydrostatic fraction of cerebrospinal fluid pressure. In the horizontal position it amounts to 50 mm. and is due to the column of cerebrospinal fluid which lies over the uppermost cerebral hemisphere and above the horizontal plane.

The vascular factor in normal cerebrospinal fluid pressure must now be considered. It has been seen above that considerable alterations in this pressure occur with respiratory and cardiac activity. It has been calculated that as the volume of intracranial venous blood fluctuates with inspiration and expiration the variation in intracranial pressure averages 40 mm. Again as the volume of intracranial arterial blood increases with cardiac systole the average rise in cerebrospinal fluid pressure amounts to 40 mm. There is thus a total variation of pressure of 80 mm. or more recurring every few seconds. It has been seen that the usual recording system will not register such rapid variations in pressure. The fluid in the manometer takes up a mean position between the two extremes and oscillates a millimetre or less on each side of this position. The vascular factor will thus add an average of 40 mm. of pressure to the 50 mm. already considered to be due to a hydrostatic factor. This average vascular fraction of 40 mm. represents one half of the average variations in cerebrospinal fluid pressure resulting from cardiac and respiratory activity. Thus the hydrostatic and vascular factors together contribute approximately 90 mm. to the normal cerebrospinal fluid pressure in the horizontal position. Since the latter averages about 120 mm. the contribution is a considerable one.

It is therefore believed that hydrostatic and vascular factors are of great importance in the maintenance of the normal cerebrospinal fluid pressure. But other factors play a part. That the balance between the production and absorption of the fluid has a bearing is obvious from several observations. In obstruction to the fluid circulation—due for example to a tumour in the posterior cranial fossa, the rate of absorption diminishes and intracranial pressure rises markedly. On the other hand the rapid removal of cerebrospinal fluid by external drainage or by the injection of intravenous hypertonic solutions will effect a speedy reduction of pressure. However, under normal conditions it is believed that the rates of production and absorption of cerebrospinal fluid will have but slight bearing on intracranial pressure and be concerned more with the regulation of the volume of cerebrospinal fluid present in the subarachnoid space at a given time.

The Circulation of the Cerebrospinal Fluid.

It is widely accepted that the cerebrospinal fluid circulates slowly and that the circulation is maintained by the forces leading to the production

and absorption of the fluid. Kubie and Fremont Smith make the important point that cerebrospinal fluid is very similar to other tissue fluids. They further suggest that Starling's description of the mechanism of the circulation of the tissue fluids can be applied to the cerebrospinal fluid circulation. Starling's theory may be briefly summarized as follows (fig. 6). In

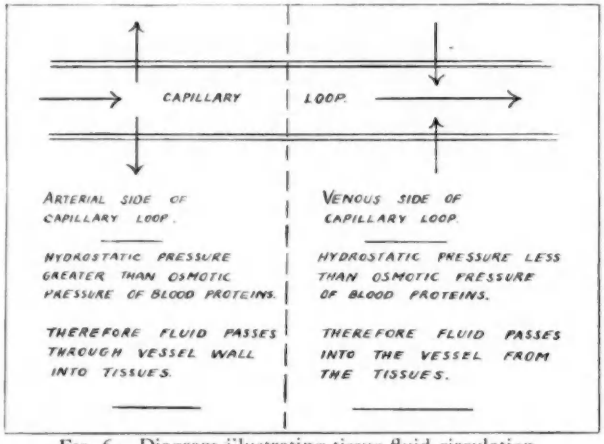
CAPILLARY
LOOP.
ARTERIAL SIDE OF CAPILLARY LOOP.
HYDROSTATIC PRESSURE GREATER THAN OSMOTIC PRESSURE OF BLOOD PROTEINS.
THEREFORE FLUID PASSES THROUGH VESSEL WALL INTO TISSUES.
VENOUS SIDE OF CAPILLARY LOOP.
HYDROSTATIC PRESSURE LESS THAN OSMOTIC PRESSURE OF BLOOD PROTEINS.
THEREFORE FLUID PASSES INTO THE VESSEL FROM THE TISSUES.

FIG. 6.—Diagram illustrating tissue fluid circulation.

the arterial side of the capillary loop vascular hydrostatic pressure (32 mm.Hg) is greater than the osmotic pressure of the blood proteins (25 mm.Hg). As a result fluid passes out of the vessel into the tissues. At the venous end of the capillary loop the vascular hydrostatic pressure (12 mm.Hg) is less than the osmotic pressure of the blood proteins and fluid therefore passes from the tissues into the lumen of the capillary. The distance between the arterial and venous ends of the capillary loop is of course microscopic and Starling's theory appears to afford a very satisfactory explanation of tissue fluid circulation. But can this theory provide an adequate explanation of the circulation of the cerebrospinal fluid through the whole extent of the subarachnoid space and between the widely separated choroid plexuses and arachnoid villi? It is believed that the theory does not provide an adequate explanation for the cerebrospinal fluid circulation and that some factor is necessary to drive the fluid through the subarachnoid space from the site of its production to that of its absorption. Further it is believed that this factor is a vascular one.

With each cardiac systole and during the period before each inspiration there is an increase in the volume of intracranial blood. Now the

volume of the cranium cannot increase, and for present purposes the nervous tissues can be regarded as incompressible and undisplaceable. Cerebrospinal fluid must therefore be displaced when the volume of the ventricles and subarachnoid space is diminished by this dilation of intracranial blood-vessels. It is believed that this displacement of cerebrospinal fluid occurs in two directions. In the first place a certain volume of fluid will be driven into the spinal canal where expansion of the dural theca allows of its accommodation. In the second place cerebrospinal fluid is driven towards the area of lowest intracranial pressure. In most normal postures—in which the head is above the level of the trunk—it is believed that pressure will be lowest in the neighbourhood of the vertex. In discussing the effect of postural alterations on cerebrospinal fluid pressure it has been pointed out that when in the erect posture the head is flexed the mean pressure in all parts of the cranium will usually be sub-atmospheric. As the head is extended however, the mean pressure in the lower part of the cranium frequently becomes greater than that of the atmosphere—although that at the vertex is still subatmospheric. It is believed from these observations that at all times when the head is above the trunk the mean pressure at the base of the skull is greater than that at the cranial vault. Further it may be pointed out that the increase in the volume of intracranial venous blood during expiration will mainly affect the venous sinuses at the base of the skull—the sigmoid sinus, lateral sinus, torcular region, &c. Blood will tend to gravitate towards these basal sinuses and the distension of them occurring during expiration is probably considerably greater than is the distension of and increase of pressure in the superior sagittal sinus at the vertex of the skull. Further the systolic expansion of the intracranial arteries will be largest in the great arteries at the cranial floor. It is thus believed that the increase in intracranial blood volume during expiration and systole will occur largely in the basal part of the cranium. This would be expected to displace cerebrospinal fluid towards the site of lowest intracranial pressure—the superior sagittal sinus along the vertex of the skull.

It is therefore believed that with every cardiac systole and every expiration the cerebral ventricles are compressed and fluid is expelled from them into the subarachnoid space. The cranial subarachnoid space is itself compressed however—especially as has been suggested above—the basal cisternæ. Cerebrospinal fluid is driven from them either into the spinal canal or towards the cranial vault.

The effect on the cerebrospinal fluid circulation of the diminished

volume of intracranial blood present during inspiration and diastole must now be considered. At this time the cerebral ventricles will enlarge, the pressure within them will fall and there will almost certainly occur a reflux of fluid into the ventricles. Since the capacity of the cranial subarachnoid space also increases—especially perhaps that of the basal cisternæ—there will be a reflux of fluid towards these cisternæ from both the spinal canal and the finer peripheral ramifications of the cranial subarachnoid space. It is almost certain that such a reflux occurs but it is believed that the reflux does not equal the efflux which precedes it. Several arguments in favour of such a view may be put forward. In the first place the finer ramifications of the subarachnoid space, especially those of the low pressure region near the superior sagittal sinus, will tend to retain a proportion of the fluid transmitted to them during systole and expiration rather than permit the regurgitation of an equal volume of fluid in the succeeding diastole and inspiration. Again when the volume of the ventricles increases during inspiration and diastole there must be a resistance to the reflux of fluid along the aqueduct. The dilatation of the ventricle and the fall in pressure in it may well result in a speeding of the production of fluid at the plexus and in this way the reflux will be smaller than the efflux. Finally the processes of production and absorption of the cerebrospinal fluid are continuous and, on the basis of Dandy's observations, rapid. If this be so the need for a rapid transfer of cerebrospinal fluid from the choroid plexuses to the arachnoid villi is obvious.

Thus it is believed that the cerebrospinal fluid circulation is aided by a vascular pump which drives fluid from the ventricles and through the cranial subarachnoid space. There may be a considerable leak back with each stroke of this pump but it is none the less considered to be of importance in the transmission of cerebrospinal fluid between the sites at which it is produced and absorbed by mechanisms which have received the attention of many workers. From what has been said it will be seen that it is considered that the spinal subarachnoid space is in the nature of a backwater off the main stream. Postural alteration as well as cardiac and respiratory movements are probably important in preventing prolonged stagnation in this situation.

Possible Applications of the Observations.

Some of the possible bearings of the observations which have been made on intracranial anatomy, physiology and pathology will now be discussed. It is believed that they may be helpful in the understanding of matters at present ill understood.

Anatomy.

In the first place the arachnoid granulations and lacunæ laterales are somewhat of anatomical mysteries. The force which causes the microscopical arachnoid villi to enlarge to form large arachnoid granulations along the superior sagittal sinus has never been understood. The many villi elsewhere in the cranium show little tendency to such enlargement but those related to this venous sinus enlarge into the period of old age and may deeply erode the skull. Again those lateral diverticula of the superior sagittal sinus—the lacunæ laterales—into which the granulations protrude are unusual structures. They, like the arachnoid granulations, are absent at birth and after this time the two develop *pari passu* as was shown by Le Gros Clarke (1920). Working in the laboratory of the late Professor Woollard, the author had an opportunity of confirming certain of Le Gros Clarke's observations (O'Connell, 1934). In addition

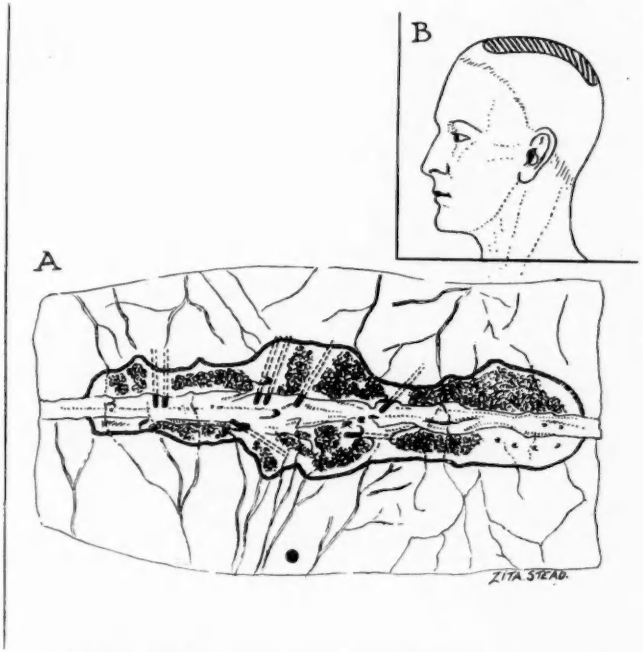

Fig. 7.—(A) Drawing of a dissection of the superior sagittal sinus showing the single lateral lacuna on each side of it. The floor of each lacuna is carpeted by pacchionian granulations. (B) Diagram to indicate the usual position of the lacunæ and pacchionian granulation (shaded area).

it was found that in later life there was but one single lacuna on each side of the superior sagittal sinus and mainly in its parietal portion. The floor of each lacuna was everywhere carpeted by arachnoid granulations (fig. 7). The suggestion was made that perhaps the lacunæ laterales developed because of the enlargement of the arachnoid granulations—the latter force causing a gradual dilatation of the small veins near the lateral angle of the sinus into which the villi project. But what was the cause of the hypertrophy of the arachnoid villi? The view that they were pathological formations or due to increased intracranial pressure could not be accepted but no alternative hypothesis could be put forward.

The following suggestion can now be made however. In the erect position and in most postures in which the head is above the level of the trunk the superior sagittal sinus—especially along the vertex—will be relatively empty, blood tending to collect in the basal sinuses. It is believed that intracranial venous pressure will be at its lowest in the uppermost part of the superior sagittal sinus and that variations in the rate of venous outflow from the skull (e.g. with respiration) will be reflected here later and to a less extent than in the basal sinuses. With each recurring elevation of cerebrospinal fluid pressure of approximately 80 mm. of cerebrospinal fluid—fluid will be driven through the subarachnoid space towards this low pressure region. It may well be that this rhythmic thrust of fluid into the arachnoid villi in relation to the superior sagittal sinus causes these villi to enlarge to form arachnoid granulations or pacchionian bodies. Further it may be that this hypertrophy of the granulations in its turn leads to the formation of the lacunæ laterales from the minute venous plexuses from which they develop.

Physiology.

In the second place the physiological applications of the observations which have been described may again be indicated. It has been suggested that vascular and hydrostatic factors are important in the maintenance of the cerebrospinal fluid pressure and that a vascular factor is important in maintaining the circulation of the cerebrospinal fluid.

Pathology.

Finally it is believed that the observations may be of value in the interpretation of certain intracranial pathological processes. In the first place they provide an explanation of the development of localized hydrocephalus in the presence of a normal or subnormal intracranial pressure.

It is widely recognized that when an area of cerebral hemisphere is injured a dilatation of the adjacent portion of the lateral ventricle into the injured area occurs. Such ventricular dilatation occurs in relation for example to areas of focal brain damage in closed head injuries (fig. 8),

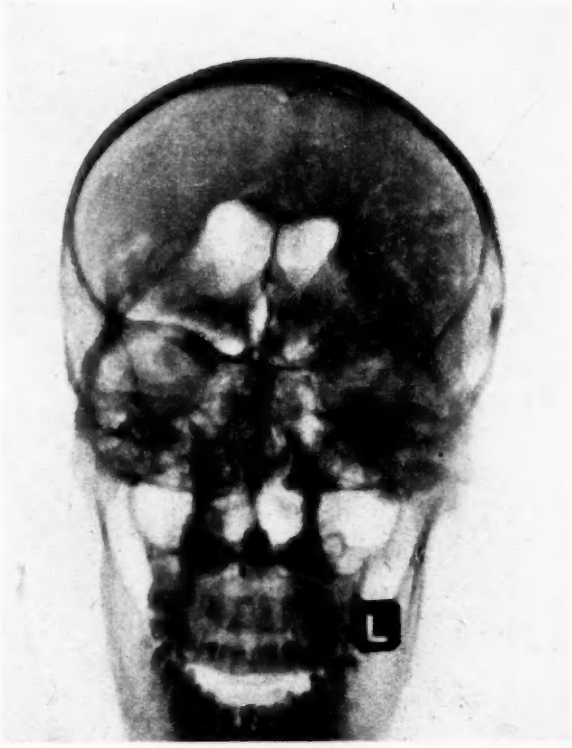

FIG. 8.—G. B. Encephalogram of a patient who had received a closed fracture of the left occipital region and a severe right fronto-temporal *contre coup* lesion. The latter had produced a left hemiparesis. The dilatation of the frontal and temporal horns of the right lateral ventricle is seen. Antero-posterior view.

a drained abscess (fig. 9) or degenerative vascular lesions (fig. 10). The dilatation will occur and progress when intracranial pressure is normal or even subnormal. Since it may be a rapid process, considerable dilatation occurring within a period of hours after tapping a brain abscess, it cannot be regarded as the effect of the traction of scar tissue

on the ventricular wall. What is the force responsible for it? It is believed that it is the regularly occurring increases in intraventricular pressure with each systole and expiration. In the normal individual when intraventricular pressure rises, as ventricular volume diminishes with this phase of cardiac and respiratory activity, all portions of the ventricular wall present an equal resistance to the increased pressure and fluid is driven from the ventricles. When an area of ventricular wall (cerebral

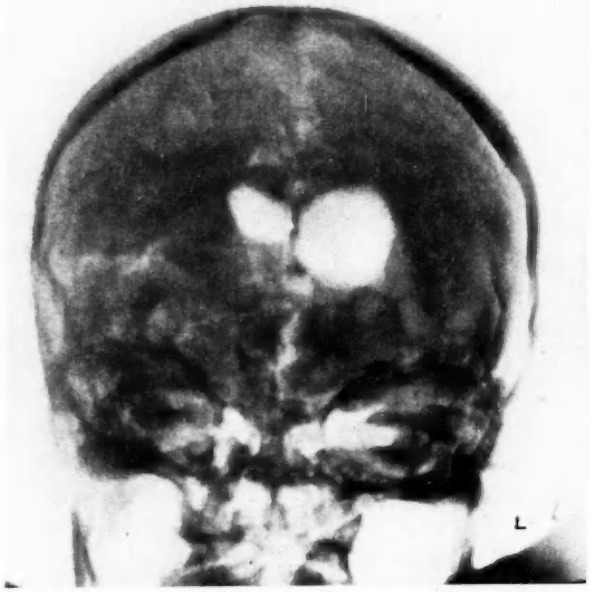

FIG. 9.—J. N. Encephalogram of a patient following drainage of a large left tempero-sphenoidal abscess. The dilatation of the left lateral ventricle especially its body and temporal horn is seen. Antero-posterior view.

hemisphere) has been injured in one way or another this portion of the wall of the ventricle will present a diminished resistance to the thrust of increased ventricular pressure corresponding to systole and expiration with the result that the ventricle will dilate in this region. Such dilatation will continue until the loss of cerebral tissue has been made good

and until all parts of the ventricular wall again present an equal resistance to the pressure thrusts to which they are subjected.

It is believed that the occurrence of localized hydrocephalus of this type may be the factor responsible for the development of traumatic cerebral fungus. Although many suggestions have been made to explain the progressive protrusion of cerebral tissue through a cranial wound none of them has as yet seemed to be adequate. In the absence of any

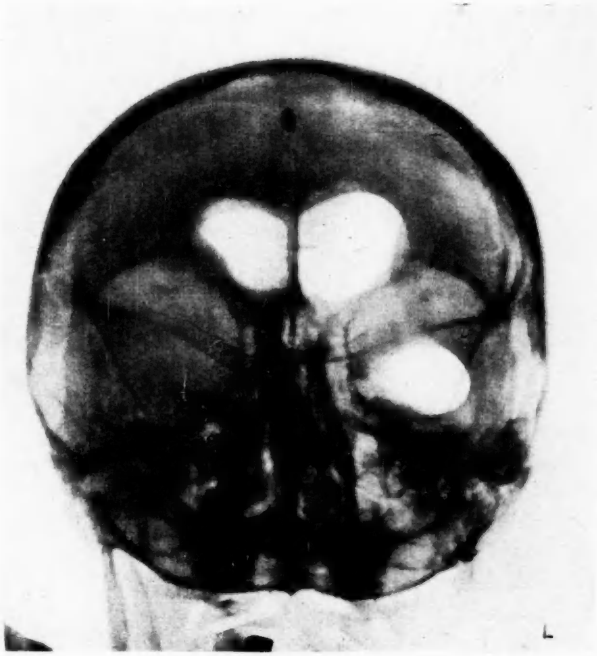

FIG. 10.—M. P. Encephalogram of patient who had developed an extensive thrombosis in the distribution of the left middle cerebral artery. With the disappearance of her hemiparesis a severe dysphasia remained. The dilatation of the ventricular system is seen. The left ventricle (especially its temporal horn) is most markedly affected. Antero-posterior view.

infective complication and in the presence of a normal intracranial pressure progressive protrusion of cerebral tissue takes place through a defect in its coverings. The following personal explanation of the mechanism of cerebral fungation was put forward in a recent paper (O'Connell, 1943). When a wound of the head destroys a considerable

area of scalp, skull and dura mater as well as penetrating the cerebrum the usual dilatation of the related portion of the lateral ventricle occurs. But the thinned ventricular wall in this region will continue to present a diminished resistance to intraventricular pressure thrusts when it reaches the level of the dural defect. It will therefore be carried through the defect and a progressively enlarging cerebral fungus will result. The treatment suggested by this theory is cerebrospinal fluid drainage. This will empty the ventricles and withdraw the fungus inside the cranium. In practice this treatment has been found to be the most efficacious. The lumbar puncture must be repeated at frequent intervals until the injured cerebral tissue has acquired sufficient rigidity to withstand the thrusts of intraventricular pressure to which it is subjected. With epithelialization of this area of granulation tissue the fungus heals.

It will be seen that these examples of localized hydrocephalus occurring in the presence of normal or subnormal intracranial pressure are readily explicable when it is known that the fluctuations in intraventricle pressure with cardiac and respiratory activity are of considerable magnitude. This knowledge also allows of a more ready understanding of the occasional development of a generalized internal hydrocephalus in the presence of normal or subnormal intracranial pressure. It is known for example that after severe closed head injuries a slowly developing hydrocephalus of mild degree may occur. Intracranial pressure may be subnormal, there is no evidence of a block in the course of the cerebrospinal fluid pathways and the patient may show gross intellectual impairment. It may well be that in this group of cases there is severe diffuse brain damage with multiple small lesions and that the dilatation of the ventricles is a measure of the amount of such damage to the hemispheres since it will progress until the whole ventricular wall presents a normal resistance to the systolic and expiratory thrusts of intraventricular pressure.

The effects of the rhythmic variations in intracranial pressure are not limited to the nervous tissues however. The skull changes to be seen in internal hydrocephalus, due for example to a posterior fossa tumour, are probably largely due to these variations. The cerebral convolutions may become imprinted upon the inner table of the skull and the dorsum of the sella turcica may be destroyed by the dilated third ventricle. It is unlikely that it is the constant pressure of nervous tissue upon bone which brings about these changes and probable that it is the pulsatile expansion of the cerebrum and its ventricles with cardiac and respiratory activity which is responsible. Mere contact with other tissues does not lead to absorption of bone. When, however, the compression of bone

by another tissue is a fluctuating one bone absorption frequently does occur. It is seen in the impressions made on bones by arteries and in the bone erosion of aneurysms. Twining (1939) hinted at the importance of pulsation in the production of sellar erosion in his Hunterian lecture in 1936.

Finally it may be pointed out that in children closed fractures of the cranial vault are sometimes attended by sequelæ not seen in the adult. At times absorption of bone occurs until the linear fracture is replaced by a wide defect through which the cerebral pulsations are transmitted to the scalp. Very occasionally the condition progresses until the rare traumatic cephalhydrocoele develops. Here a cystic swelling forms at the site of injury and apparently the swelling usually contains a prolongation of the lateral ventricle. It is therefore sometimes referred to as a ventricular cyst. Such sequelæ of head injuries in children have in the past been difficult to understand but the following explanation may now be put forward. A fracture of the skull vault in a child may be unassociated with a scalp wound and yet because of the relatively unresistant skull a dural tear and severe focal cerebral damage may be produced. As described above the lateral ventricle dilates into the damaged area of cerebrum and the diverticulum projects into the dural tear. If the latter be small the only consequence will be local bone absorption at the fracture site; if the dural tear be large, however, the pulsation of the ventricular diverticulum will produce a wide area of bone absorption and a cephalhydrocoele will thus be constituted. It is of course possible that in cases of traumatic cephalhydrocoele some additional factor is at work—for example an obstruction to the cerebrospinal fluid circulation. In the only personal case observed such an obstruction was present, there being a tumour in the 3rd ventricle.

Summary.

(1) The modern conception of intracranial pressure and the cerebrospinal fluid circulation is described and its development is reviewed.

(2) The observation has been made that when cerebrospinal fluid pressure is measured in the horizontal position after death it is, at least frequently, not greater than that of the atmosphere.

(3) The variations in cerebrospinal fluid pressure with cardiac and respiratory activity have been measured. The influence of the system used in recording these variations has been demonstrated. Experiments have been made which show that the cardiac and respiratory variations in cerebrospinal pressure are of considerably greater magnitude than is generally realised.

(4) The variations in cerebrospinal fluid pressure with postural alteration have been observed.

(5) Normal cerebrospinal fluid pressure—as measured in the horizontal position—is analysed and it is believed that vascular and hydrostatic factors are of importance in its maintenance.

(6) From a consideration of the observations which have been made it is suggested that a vascular factor is important in maintaining the cerebrospinal fluid circulation.

(7) In addition to these physiological implications of the observations which have been described, some of their possible anatomical and pathological applications are considered.

In conclusion I must express my gratitude to those who have helped me in this work. Mr. Leonard Kingdom, my house surgeon, has assisted me with several of the experiments. Professor Paterson Ross has helped me in many ways, especially in being always ready to give of his time to hear and discuss my ideas with me. Finally the late Professor Woollard first interested me in the problems which have been considered. If there is anything of interest in my remarks I am glad that they have provided me with an opportunity to recall his memory and my debt to him.

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THE MARCHI REACTION: ITS USE ON FROZEN SECTIONS AND ITS TIME LIMIT.

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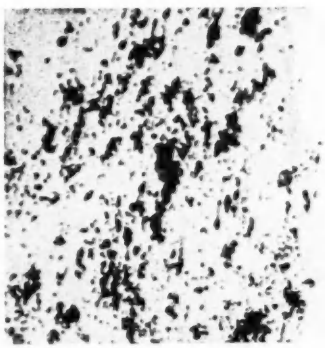
SEVERAL interesting contributions of recent date have been made to a critical discussion of the Marchi method (e.g. Mettler, 1932, Swank and Davenport, 1934, 1935, Weisschedel and Jung, 1939). The most important papers on this subject are those by Swank and Davenport, because they provide the experimental neurologist with a new and simplified technique which is briefly as follows: (1) the animal is killed by an overdose of nembutal; (2) fixation of the brain for forty-eight hours in 10 per cent. formalin; (3) slices are cut and, without washing, put in the following solution: 1 per cent. aqueous solution of $KCLO_3$ 60 c.c.; 1 per cent. aqueous solution of osmic acid 20 c.c.; glac. acetic acid 1 c.c.; 37 per cent. formaldehyde 12 c.c. After staining for seven to ten days the slices are washed for twelve hours, dehydrated and embedded in celloidin.

To save time and labour we have tried the method of Swank and Davenport with frozen sections and have found the following slight modifications very useful: Fixation for not more than forty-eight hours in 10 per cent. formalin (neutral). Slices are cut and washed for ten minutes in a 1 per cent. $KCLO_3$ solution, thus removing an excess of formalin which occasionally seems to cause a staining of normal fibres. After this the slices are put into the Marchi solution advocated by Swank and Davenport, and left there for about ten days. They are washed in running water for several hours and then cut on a freezing microtome. The thickness of the sections may be from 60μ to 90μ, and for serial arrangement they can be treated after sectioning like celloidin sections. A convenient method is to put the sections in five dishes filled with distilled water, so that the first dish contains the first, sixth, and eleventh sections and so forth. The sections can be arranged in any manner to suit individual requirements and can be counterstained with toluidin blue or light green, the latter being preferable because it does not fade as quickly as toluidin blue. All sections can be mounted and accounted for and there need be no fear of losing a section if appropriate care is taken. We prefer to

transfer the sections after cutting to 96 per cent. alcohol for half an hour. After this they are cleared in a bath of creosote. The excess of creosote is poured back into stock. The sections are blotted with filter paper and become perfectly flat. They are mounted with Canada balsam and covered by a cover glass. Sections treated in this way have kept well-defined Marchi staining for more than eighteen months.

In examining these sections with the microscope the degenerated fibre tracts are clearly outlined, and even the very thinly myelinated fibres are distinctly shown. The background is transparent and bright, the normal fibres are unstained, and "pseudo-Marchi" granules are only rarely present. Only in cases where nerve roots have been pulled can pseudo-Marchi degeneration be seen. This type of degeneration is found almost invariably in the optic tracts and has been widely discussed by Mettler (1932).



TEXT-FIGURE 1.—Positive Marchi reaction in the internal capsule from a section of a rabbit's brain in which a cortical lesion had been made eight months previously. Note the well-defined Marchi granules still occupying the old fibre pathway. No significant removal of the débris has begun. The clear area on the right of the photomicrograph is the caudate nucleus. X 140.

The time limit in which an optimum Marchi reaction is said to be obtained varies somewhat in the literature. Swank and Davenport recommend for rabbits about ten days. Weisschedel and Jung obtained good results in cats eight days after operation. Mettler states that it is the custom in his laboratory to remove the brain eleven days after operation. We found in rabbits and cats that these times seem rather short. We have gained the impression that the optimum reaction is at least three weeks. For staining finer fibres such as those of the callosal

system, it is certainly advisable to give a longer time than eleven days. The time allowed for degeneration has become rather shortened in recent years, as is apparent in recent publications, due to the fear that the removal of the Marchi granules after a certain time may interfere with the interpretation of the picture. The question arises therefore, how long is it safe to use the Marchi technique after operation. We found that in rabbits excellent results can be obtained even after eight months. The removal of the fatty débris is a very slow process and this process of removal can be distinguished from the pattern of degenerated fibres because it follows the vascular system. In counterstaining such a section with toluidin blue the phagocytic cells are seen to be transporting the fat granules to the vascular wall. It is also common to see the endothelial cells of the capillaries clearly outlined by their inclusion of fatty granules, and very numerous fat droplets in the choroid plexus are visible.

Another important question is the time which should be allowed for the complete removal of the myelin débris. We have found in cats and rabbits that a positive reaction with osmic acid for degenerated fibres can still be obtained after a year, in spite of the current opinion that the removal of the degenerated products has considerably advanced after two months. This observation is of the greatest importance for experiments in which a second lesion is superimposed on the same animal in the hope that the débris of the first injury has been cleared away. Experiments of this type have been carried out with the purpose of eliminating, by the process of degeneration and subsequent resorption, fibres of cortical origin to lower centres of the brain or spinal cord. For example, in the internal capsule there are descending fibres partly of cortical and partly of subcortical origin. In order to study the subcortical fibres, attempts have been made to eliminate the cortical fibres by a preliminary destruction of the cortex, and allowing a few months to elapse for the complete resorption of the degenerated fibres. However, it would be very difficult in the first six months at least to be certain whether Marchi degeneration seen in sections of the material is the result of the first or second operation. Even by the end of one year the Marchi granules resulting from the first lesion may still be seen, though transformed into a very fine, dust-like deposit. It seems doubtful, therefore, whether some authors have been correct in the interpretation of a positive Marchi reaction which was thought to be due entirely to a second lesion. It has clearly not been fully realized how slow the removal of the degeneration products of the first lesion may be.

On the other hand, there is also an advantage in the fact that the

disappearance of the Marchi granules is so long retarded, for neurologists and pathologists may profitably use a Marchi stain in investigations in the study of even comparatively long-standing lesions. The Marchi reaction resulting from a lesion superimposed on an animal operated a year previously can sometimes be distinguished from the effects of the primary lesion by the fact that the staining is more intense and the osmic granules coarser and more compact. Such a distinction, however, is by no means always clear.

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Notices of Recent Publications

Behaviour and Neurosis: An Experimental Psychoanalytic Approach to Psychobiologic Principles. By J. Masserman, University of Chicago Press. 1943. Pp. 269.

To the neurologist the main interest of this book is its record of the author's skilful and well-designed experiments on the hypothalamus; experiments which have shorn this structure of some of the hypothetical functions with which it has been verbally endowed by the uncritical work and enthusiasm of a number of experimental and clinical workers. The volume opens with an historical and purposive introduction covering the theories of behaviour current from the classic Greek period to our own time. The reader should not be discouraged by this chapter with its florid exuberance of philosophical terminology and psychological neologisms and its highly stilted writing. When he comes to record his observations, the author happily lapses into a more direct and natural speech.

His intention was to determine whether the complex manifestations provoked by electrical stimulation of the hypothalamus in the cat, spoken of by Sherrington as "pseudaffective" and more recently by Bard as "sham rage," were accompanied by any relevant and appropriate mental experience: in other words, whether the hypothalamus is "an afferent, experience-mediating" organ. That it is such an organ has been claimed for it, not only in respect of emotional experience, but it has also been suggested that it is the "level of final integration within the nervous system" from which impulses ascend to the cerebral cortex to awaken its activity. This implies a predominant role in the mediation of consciousness for the hypothalamus. Masserman's experiments prove conclusively that the hypothalamus is a purely efferent organ and does not form the anatomo-physiological substratum of "consciousness" or "experience." It merely organizes the somatic expressions of fear and rage, and under experimental conditions these expressions may be produced without the normally accompanying emotions of the intact animal.

Masserman's conclusions are summarized as follows: (i) The hypothalamus may integrate and possibly reinforce the effector neural impulses controlling some of the sympathetic and motor manifestations of rage and fear; however, there is little or no basis for the thesis that the hypothalamus governs or even mediates the emotional experiences themselves; (ii) a direct psychosomatic relationship between hypothalamic function affective experience probably does not exist, as (*a*) the reactions to stimulation of the hypothalamus do not greatly modify emotional behaviour; (*b*) animals with extensive destructive lesions of this structure react to emotional stresses and appear to experience genuine affective states; and (*c*) animals subjected to prolonged "conditioning" in which sensory signals precede hypothalamic stimulation do not learn to respond to either sensory or hypothalamic stimuli as they do to spontaneous or experimental situations of adequate emotional significance; (iii) the clinical and pathological evidence as to the role of the human hypothalamus in emotional experience is inadequate; and (iv) the hypothalamus co-ordinates the neural and humoral mechanisms of conative and emotional expression.

In this, as in other writings dealing with "consciousness," we find the tendency to regard this abstraction as referring to an elementary and unitary state. It might be more accurate to say that there are parts of the brain that function consciously, and then to bear in mind that there may be more than a single category and a single site of conscious functioning. Kleitman ("Sleep and Wakefulness," Chicago University Press, 1939) in his evolutionary hypothesis of sleep, perhaps the most penetrating statement of the problem we possess, draws a distinction between a consciousness of choice and a consciousness of necessity; the latter being that variety of awareness possessed by the decorticated dog; an awareness virtually restricted to internal states of the animal and conditioned by these, while the consciousness of choice—that of the intact organism—is related to the environment.

It seems likely that if the hypothalamus does function in any measure consciously—and Masserman's experiments afford no indication that it does—this function could be no more than Kleitman's "consciousness of necessity," while the hypothesis that the hypothalamus activates the cerebral cortex by way of afferent paths comes to grief—as Masserman points out—because no afferent hypothalamic-cortical pathway is known to exist. It seems, therefore, that any hopeful approach to the identification of the parts of the brain that function consciously is a more precise analysis of what we intend by the term "consciousness." This is not yet a term of precision, and until it becomes so expositions of its nature and "seat" can be no more than rhetorical flights.

In other chapters, the author subjects the experiments of Pavlov, and particularly the Russian physiologist's deductions from these, to a critical analysis. He has provided a valuable and most suggestive book.

Borderlands of Psychiatry. By STANLEY COBB, Harvard University Press, Cambridge, Mass. 1943. Pp. 166. Price $2.50.

Under this title the author has published a series of essays on the borderland between the psychological and the physiological fields. The reader will find them interesting and suggestive, whether his interests are psychological or neurological. It is a vast and complex subject that Professor Cobb deals with, and it is possible that neither category of reader will agree with all his conclusions, but no one will read them without profit, and they will have served their purpose if they help to break down the barriers of incomplete knowledge and of prejudice that hinder the workers in either field from a clear perspective of the conjoined territory.

The psychologist is reminded that after all the brain is the organ of mind and that some measure of familiarity with the anatomy and physiology of this organ must surely be essential to a balanced psychological outlook. The neurologist, on the other hand, may learn that the line dividing psychogenic from physiogenic disorders is not so firmly drawn as he may have supposed. The book opens with a series of clinical case records exemplifying this last point. There is a valuable critical chapter which deals with the results of what has come to be called prefrontal leucotomy, an operation that the author considers unjustified except for irrecoverable subjects of 60 years or over, and he deprecates its use for young recoverable psychotics or psychoneurotics.

The sudden enthusiasm for physical remedies in the treatment of the neuroses and psychoses by which the psychiatrical world now seems carried away is the most remarkable phenomenon in medicine to-day. For at least a quarter of a century, hypotheses of the psychogenesis of these disorders have been formulated

and elaborated in a very considerable literature, and have been accompanied by psychological techniques for their relief and cure that have received an equal publicity and have been the subject of far-reaching claims. Yet now an ever increasing proportion of sufferers from neuroses and psychoses are being subjected by the psychiatrist to convulsive therapy and to amputation of the frontal poles. If belated, this recognition of the brain as the organ of mind has been signalized by widespread physical attacks upon its integrity. It is not easy to understand how all this accords with the trend of psychological doctrines as we have been so familiar with them, and upon this *volte face* Professor Cobb is tactfully silent.

In other chapters the author deals with the visual, motor and sensory functions of the brain and with speech, and also devotes chapters to the neuroses and psychoneuroses.

The popular character of these essays, as the author names them, leads him at times into odd extravagances of statement: thus "poets are always years, if not centuries, ahead of scientists. They see and understand what goes on; the scientist labours along in the rear, trying to explain why it goes on." But surely, the aims of the poet and the scientist are wholly different. The poet is concerned with ethical and æsthetic values, and with the expression in predominantly emotive language of his reactions to what goes on. The scientist is concerned with the "how" and not with the "why," and as far as he is able he eschews emotive language. However, these flamboyances are the pitfalls that beset the feet of the popular lecturer who combines both emotive and referential language: a combination that makes for poor poetry and not for good science.

Nevertheless, the reader may spend a pleasant and a profitable week-end with this volume of essays.

The Nature of Explanation. By K. J. W. CRAIK. Cambridge University Press. 1943. Pp. 121. Price 6s.

The simple biologist imperfectly familiar with the terminology of philosophy and that of the mystical quasi-philosophy that modern physics has become will find the opening four chapters of this monograph on current theories of explanation very heavy going, but thereafter he will find the author's theme that the nervous system may be viewed much as a calculating or predicting machine that is capable of modelling or paralleling external events an extremely interesting one. Taking for granted that the external world and causation exist, he points out that one of the fundamental properties of thought is its capacity to predict events. This enables us to predict consequences of recondite physical and chemical processes, and in the practical sphere to design a bridge with the requisite factor of safety for the work required of it without first building at hazard by the method of trial and error. In its simplest terms the process of thought involved is the observation of some external event or process. The event or process is "translated" into words, numbers or other symbols. By a process of deduction other symbols are reached by reasoning, inference, &c., and these symbols are finally re-translated into external processes (as in building a bridge to a design), or into a recognition of the correspondence between these symbols and external events (as in realizing that a prediction is fulfilled).

He then points out that certain calculating machines (e.g. Kelvin's tidal predictor) show the same ability. The analogy betwteen the calculating machine and the nervous system is then developed, and the relation of neural activity to thought discussed.